neurotransmitter receptors. Thus, changes in calcium ion concentration could lead to alterations in neural functions.

Bawin et al. [1975] reported an increase in efflux of calcium ions from chick brain tissue after 20 min of exposure to a 147-MHz RFR (1 to 2 mW/cm^2). The effect occurred when the radiation was sinusoidally amplitude-modulated at 6, 9, 11, 16, or 20 Hz, but not at modulation frequencies of 0, 0.5, 3, 25, or 35 Hz. The effect was later also observed with 450-MHz radiation amplitude-modulated at 16 Hz, at a power density of 0.75 mW/cm^2. Bicarbonate and pH of the medium were found to be important factors in the effect [Bawin et al., 1978].

In vitro increase in calcium efflux from the chick brain was further confirmed by Blackman et al. [1979, 1985, 1980a,b] using amplitude-modulated 147-MHz and 50-MHz RFR. They also reported both modulation-frequency windows and power windows in the effect. These data would argue against a role of temperature. The existence of a power-density window on calcium efflux was also reported by Sheppard et al. [1979] using a 16-Hz amplitude-modulated 450-MHz field. An increase in calcium ion efflux was observed in the chick brain irradiated at 0.1 and 1.0 mW/cm^2, but not at 0.05, 2.0, or 5.0 mW/cm^2.

Two other papers reported no significant change in calcium efflux from the rat brain irradiated with RFR. Shelton and Merritt [1981] exposed rat brains to 1000-MHz RFR pulse-modulated with square waves (16 and 32 Hz, power density 0.5-15 mW/cm^2). They observed no change in calcium efflux from the tissue. Merritt et al. [1982] exposed rat brains with either 1000-MHz pulsed radiation modulated at 16 Hz at 1 or 10 mW/cm^2 (SARs 0.29 and 2.9 W/kg), or to a pulse-modulated 2450-MHz RFR at 1 mW/cm^2 (SAR 0.3 W/kg). No significant change in calcium efflux was observed in this experiment. These researchers also exposed animals, in vivo, injected with radioactive calcium to pulsed 2060-MHz RFR at different combinations of intensities and pulse repetition rates. No significant change in radioactive calcium content was found in the brains of the animals after 20 min of exposure. It is not known whether the discrepancies between these data and the findings of Bawin et al. [1975, 1978] and Blackman et al. [1979] were due to the use of square-wave instead of sinusoidally modulated radiation or due to the different species of animals studied. Electromagnetic field-induced increases in calcium efflux have also been reported in tissues obtained from different species of animals. Adey et al. [1982] observed an increase in calcium efflux from the brain of conscious cats paralyzed with gallamine and exposed for 60 min to a 450-MHz field (amplitude modulated at 16 Hz at 3.0 mW/cm^2, SAR 0.20 W/kg). Lin-Liu and Adey [1982] also reported increased calcium efflux from synaptosomes prepared from the rat cerebral cortex when irradiated with a 450-MHz RFR amplitude-modulated at various frequencies (0.16-60 Hz). Again, modulation at 16 Hz was found to be the most effective. More recently, Dutta et al. [1984] reported radiation-induced increases in calcium efflux from cultured cells of neural origins. Increases were found in human neuroblastoma cells irradiated with 915-MHz RFR (SARs 0.01-5.0 W/kg) amplitude-modulated at different frequencies (3-30 Hz). A modulation frequency window was reported. Interestingly, at certain power densities, an increase in calcium efflux was also seen with unmodulated radiation. A later paper [Dutta et al., 1989] reported increased calcium efflux from human neuroblastoma cells exposed to 147-MHz RFR amplitude-modulated at 16 Hz. A power window (SAR between 0.05-0.005 W/kg) was observed. When the radiation at 0.05 W/kg was studied, peak effects were observed at modulation frequencies between 13-16 Hz and 57.5-60 Hz. In addition, the authors also reported increased calcium efflux in another cell line, the Chinese hamster-mouse hybrid neuroblastoma cells. Effect was observed when these cells were irradiated with a 147-MHz radiation amplitude-modulated at 16 Hz (SAR 0.05 W/kg).

In more recent studies, Blackman explored the effects of different exposure conditions [Blackman et al., 1988, 1989, 1991]. Multiple power windows of calcium efflux from chick brains were reported. Within the power densities studied in this experiment (0.75-14.7 mW/cm^2, SAR 0.36 mW/kg per mW/cm^2) narrow ranges of power density with positive effect were separated by gaps of no significant effect. The temperature in which the experiment was run was also reported to be an important factor of the efflux effect. A hypothetical model involving the dynamic properties of cell membrane has been proposed to account for these effects [Blackman et al., 1989].

In addition to calcium ion, changes in other trace metal ions in the central nervous system have also been reported after RFR exposure. Stavinoha et al. [1976] reported an increase in zinc concentration in the cerebral cortex of rats exposed to 19-MHz RFR. Increases in the concentration of iron in the cerebral cortex, hippocampus, striatum, hypothalamus, midbrain, medulla, and cerebellum; manganese in the cerebral cortex and medulla; and copper in the cerebral cortex were reported in the rat after 10 min of exposure to 1600-MHz RFR at 80 mW/cm^2 (SAR 48 W/kg) [Chamness et al., 1976]. The significance of these changes is not known. The effects could be as a result of hyperthermia, because the colonic temperature of the animals increased by as much as 4.5 ^{o}C after exposure.

RADIOFREQUENCY RADIATION AND THE ACTIONS OF PSYCHOACTIVE DRUGS

The actions of psychoactive drugs depend on the functions of the neurotransmitter systems in the brain. Changes in neurotransmitter functions after RFR exposure will inevitably lead to changes in the actions of psychoactive drugs administered to the animal. On the other hand, if there is no change in the pharmacokinetics of drugs after RFR exposure, observed changes in psychoactive drug actions would imply RFR-induced changes in neurotransmitter functions in the animal. Pharmacological studies of RFR effects provide an important insight into the neural mechanisms affected by exposure to RFR.

Psychoactive drugs of various types have been tested in animals after exposure to RFR. Since an effect of RFR is to increase the body temperature of an animal, special attention has been given to study the effects of psychoactive drugs on the thermal effect of RFR. Jauchem [1985] has reviewed the effects of drugs on thermal responses to RFR. Radiofrequency radiation of high power densities was used in these studies.

Some psychoactive drugs have a profound effect on thermoregulation and, thus, alter the body temperature of an animal upon administration. The effect could be due to direct drug action on the thermoregulatory mechanism within the central nervous system or effects on autonomic functions such as respiration, cardiovascular and muscular systems, which lead to changes in body temperature. Several studies have investigated the neuroleptic (anti-psychotic) drug, chlorpromazine. Michaelson et al. [1961] reported that chlorpromazine enhanced the thermal effect of RFR in dogs (2800 MHz, pulsed, 165 mW/cm^2). Drug-treated animals had a faster rate of body temperature increase and a higher peak temperature when irradiated with RFR. Similar effects were seen with pentobarbital and morphine sulfate. On the other hand, Jauchem et al. [1983, 1985] reported that chlorpromazine attenuated the thermal effect of RFR in ketamine anesthetized rats. The drug slowed the rate of rise in colonic temperature (from 38.5-39.5 ^{o}C) and facilitated the return to base line temperature after exposure to RFR (2800-MHz, 14

W/kg); however, when the body temperature was allowed to rise to a lethal level, chlorpromazine potentiated the effect of RFR. Interestingly, haloperidol, another neuroleptic drug, was found to have no significant effect on RFR-induced change in colonic temperature. In another study [Lobanova, 1974b], the hyperthermic effect of RFR (40 mW/cm^2) was found to be attenuated by pretreatment with chlorpromazine or acetylcholine and enhanced by epinephrine and atropine (a cholinergic antagonist). This suggests a role of acetylcholine in modifying RFR-induced hyperthermia. Indeed, Ashani et al. [1980] reported that acute RFR exposure (10 min at 10 mW/cm^2) enhanced the hypothermic effects of AChE inhibitors. On the other hand, Jauchem et al. [1983, 1984] observed no significant effect of atropine and propranolol (an adrenergic antagonist) on the hyperthermia produced in ketamine anesthesized rats exposed to 2800-MHz RFR (SAR 14 W/kg).

Several studies investigated the effects of RFR on the actions of barbituates. Barbituates are sedative-hypnotic compounds, which produce narcosis (sleep states and loss of consciousness), synchronization of EEG, and poikilothermia (i.e., loss of body temperature regulatory functions). Baranski and Edelwejn [1974] reported that acute exposure to pulsed RFR (20 mW/cm^2) had little effect on the EEG pattern of rabbits given phenobarbital; however, after 200 h of exposure (at 7 mW/cm^2), desynchronization rather than synchronization of the EEG pattern was seen after phenobarbital administration. Rabbits anesthetized with pentobarbital and subjected to 5 min of RFR (0.7-2.8 mW/cm^2) showed periods of alternating EEG arousal (desynchronization) and sedation (synchronization) and periods of behavioral arousal. The duration of EEG arousal seemed to correlate with the power density of RFR [Goldstein and Sisko, 1974].

Wangemann and Cleary [1976] reported that short term RFR exposure (5-50 mW/cm^2) decreased the duration of pentobarbital induced loss of righting reflex in the rabbit. The investigators speculated that the effect was due to the thermal effect of RFR, which decreased the concentration of pentobarbital in the central nervous system. Supporting this, Bruce-Wolfe and Justesen [1985] reported that warming an animal with RFR while under anesthesia could attenuate the effects of pentobarbital. Mice exposed to continuous-wave 2450-MHz RFR at 25 and 50 mW/cm^2 also showed a power density-dependent reduction in the duration of hexobarbital-induced anesthesia [Blackwell, 1980]. On the other hand, Benson et al. [1983] reported decreased onset-time and prolonged duration of phenobarbital-induced narcosis in mice after exposure to RFR (10 mW/cm^2, 10 min). They showed that the effect was caused by an increase in deposition of phenobarbital in the brain. We [Lai et al., 1984a] have shown that after 45 min of exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, whole-body average SAR 0.6 W/kg), the pentobarbital-induced narcosis and hypothermia in the rat were enhanced. We also found that exposure of rats in two different orientations (with the head of the rat facing or away from the source of the RFR) had different effects on the pentobarbital-induced hypothermia, even though the average whole body SAR was similar under the two conditions. These data suggest that the pattern of localized SAR in the body of the animal might be an important determinant of the outcome of the effect.

When the body temperature of an animal is raised above a certain level, convulsions result. Various psychoactive drugs were studied in an attempt to alter the convulsive effect of RFR. Studies have also been carried out to investigate whether RFR exposure altered the potency of convulsants. It was reported that the susceptibility of rats to the convulsive effect of RFR (14 mW/cm^2, 2 h) was decreased by chloral hydrate, sodium pentobarbital, and bemegride, and enhanced by chlorpromazine, epinephrine, atropine, acetylcholine, nicotine, and monoamine oxidase inhibitors, but was not significantly affected by serotonin [Lobanova, 1974a]. Some of these results can be explained by the pharmacological properties of the drug tested. Pentobarbital and chloral hydrate are hypnotic agents and are known to have anticonvulsant effects. Chlorpromazine, nicotine, and monoamine oxidase inhibitors can lower the seizure threshold or induce convulsions depending on their dosages. Atropine, a cholinergic antagonist, has been shown to enhance the seizure threshold. It is puzzling that bemegride decreased RFR induced seizures, since it is a nervous system stimulant with similar pharmacological actions as the convulsant pentylenetetrazol.

Exposure to pulsed RFR (7 and 20 mW/cm^2) was reported to affect the effects of the convulsants, pentylenetetrazol and strychnine, on EEG activity [Baranski and Edelwejn, 1974]. Another study showed that low-level RFR altered the sensitivity of animals to the seizure inducing effect of pentylenetetrazol [Servantie et al., 1974]. Rats and mice were subjected to 8-36 days of pulsed RFR (3000 MHz, 0.9-1.2 μs pulses, 525 pps, 5 mW/cm^2). No significant change in susceptibility to the drug was seen after eight days of exposure; however, a decrease in susceptibility was observed after 15 days, and an increase in susceptibility was observed after 20, 27, and 36 days of irradiation. Mice became more susceptible to the convulsive effect of pentylenetetrazol and more animals died from convulsions. Thus, the sensitivity of the nervous system to the convulsive action of the drug changed as a function of the duration of exposure. In another study, Pappas et al. [1983] showed in the rat that acute (30 min) exposure to 2700-MHz pulsed RFR at 5, 10, 15, and 20 mW/cm^2 (SARs 0.75, 1.5, 2.25, and 3.0 W/kg, respectively) produced no significant interaction effect on pentylenetetrazol induced seizure or the efficacy of chlordiazepoxide (an anticonvulsant) to block the seizure.

Drugs affecting cholinergic functions in the nervous system have also been studied. Chronic RFR-exposed rats (10-15 days) were found to be less susceptible to the paralytic effect of curare-like drugs, which block nicotinic cholinergic transmission. A similar effect was observed on muscle preparations from the irradiated rats. Presumably, the cholinergic transmission in the neuromuscular junction was affected by RFR. Ashani et al. [1980] reported that acute pulsed RFR (10 min, 10 mW/cm^2) enhanced the hypothermic effects of an inhibitor of AChE (the degradation enzyme of acetylcholine). The site of this effect was determined to be located inside the central nervous system. Monahan [1988] also reported that RFR (2450 MHz, continuous-wave, whole body SARs 0.5-2.0 W/kg) affected the actions of scopolamine, a cholinergic antagonist, and physostigmine, a cholinergic agonist, on motor activity of mice in a maze. The data suggested enhancement of cholinergic activity after RFR irradiation.

Several studies investigated the actions of benzodiazepines, a group of drugs used for anticonvulsion, sedation-hypnosis, and antianxiety purposes. Two of the most commonly used benzodiazepines for the treatment of anxiety disorders are chlordiazepoxide (Librium) and diazepam (Valium). Low-level pulsed RFR (1 mW/cm^2, whole body SAR 0.2 W/kg) potentiated the effect of chlordiazepoxide on bar-pressing behavior of rats working on a DRL-schedule for food reinforcement; however, the same authors also reported no interaction effects between RFR and diazepam on bar pressing [Thomas et al., 1979, 1980].

Increase in brain benzodiazepine receptors in the brain after RFR exposure [Lai et al, 1992a] could explain the former effect. A possible explanation for the discrepancy of the results observed with chlordiazepoxide and diazepam was that diazepam has a higher potency than chlordiazepoxide. The potency of diazepam that was effective in attenuation of experimental conflict, an animal model of anxiety, was about four times that of chlordiazepoxide [Lippa et al., 1978], and the in vitro relative affinity of diazepam with benzodiazepine receptors was 30-65 times that of chlordiazepoxide [Braestrup and Squires, 1978; Mohler and Okada, 1977]. The ranges of diazepam and chlordiazepoxide used in the Thomas studies [Thomas et al., 1979, 1980] were 0.5-20 and 1-40 mg/kg, respectively. Thus, the doses of diazepam studied might be equivalent or higher in potency than the highest dose of chlordiazepoxide used. This supposition was supported by the observation in the Thomas studies that the effects of the two drugs were different. The dose-response curve of chlordiazepoxide on the DRL-schedule operant responses showed a dose-dependent inverted-U function, i.e., potentiation at medium dose, attenuation at higher dose, and only the portion of the response-curve that showed potentiation was affected by RFR [Thomas et al., 1979]. In the study of Thomas et al. [1980] on diazepam, only attenuation of DRL-responses was observed. Thus, the dose range of diazepam used in the study was at the attenuation portion of the dose-response function, which is not affected by RFR. These dose-dependent potentiation and attenuation effects of benzodiazepines on the operant response may involve different neural mechanisms. Radiofrequency radiation may only affect and enhance the potentiating and not the attenuating effect of benzodiazepines, which is possible because our research [Lai et al., 1992a] showed that the effect of RFR on benzodiazepine receptors is brain-region selective. Thus, the data of Thomas et al. [1979, 1980] on the interaction of RFR irradiation on benzodiazepine actions could be explained by a selective increase in benzodiazepine receptors in different regions of the brain. Another possibility is that RFR affects only the subtype of benzodiazepine receptors related to antianxiety effect and not another subtype related to the sedative-hypnotic action of the drugs. In the dose-response curve of benzodiazepine on DRL-schedule maintained behavior, the potentiation portion may be due to the former receptor subtypes and the attenuation portion the latter subtype. There is ample evidence suggesting that different subtypes of benzodiazepine receptors subserve antianxiety and sedative effects [Polc, 1988].

In addition to the above studies on the effect of RFR on benzodiazepines, Monahan and Henton [1979] trained mice to avoid or escape from 2450-MHz RFR (45 W/kg) under an avoidance paradigm. They reported that pretreatment of the animals with chlordiazepoxide decreased the avoidance response and increased the escape responses, which led to an increase in the animal's cumulative exposure to RFR after the drug treatment. The authors speculated that RFR potentiated the effect of chlordiazepoxide and caused a decrement in the avoidance response. It is also interesting that in the procedure the presence of RFR was signalled simultaneously with a tone and the animal could elicit an avoidance response, which resets the timer and delays the further presentation of RFR. Thus, the procedure had both signalled and continuous avoidance components. However, the data indicate that the effect was more like a continuous avoidance paradigm. Generally, anxiolyltic agents like benzodiazepines decrease both avoidance and escape behavior in a signalled-avoidance paradigm, but they can selectively decrease the avoidance response and leave the escape responding intact under a continuous avoidance paradigm.

Johnson et al. [1980] reported that repeated exposure (twenty-one 45-min sessions) to RFR (2450 MHz, pulsed, average whole body SAR 0.6 W/kg) reduced the sedative hypnotic effect, but increased the feeding behavior induced by diazepam. Hjeresen et al. [1987] reported that the attenuation effect of a single (45 min) RFR exposure (2450 MHz, CW, average whole body SAR 0.3 W/kg) on ethanol-induced hypothermia was blocked by treating the rat with the benzodiazepine antagonist, RO 15-1778. The data indicated that benzodiazepine receptors in the brain might mediate the effects of RFR on ethanol-hypothermia. In a more recent study, Quock et al. [1990] investigated the influence of RFR exposure on the effect of chlordiazepoxide on the stair-case test for mouse, a test for both the sedative and antianxiety effects of benzodiazepines. They reported that acute exposure (5 min at a whole body average SAR of 36 W/kg) caused a significant reduction of the sedative, but not the antianxiety effect of chlordiazepoxide. The effect was probably related to hyperthermia. Some of the above effects of RFR on benzodiazepine actions can be explained by our finding [Lai et al., 1992a] that acute RFR exposure increased benzodiazepine receptors in selective regions of the brain and that adaptation occurred after repeated exposure.

On the other hand, central benzodiazepine receptors can also affect seizure susceptibility in animals. Benzodiazepines are widely used as anticonvulsants. Exposure to RFR has been shown to affect seizure and convulsion susceptibility in animals. For example, Stverak et al. [1974] reported that chronic exposure to pulsed RFR attenuated audiogenic seizures in seizure-sensitive rats. Servantie et al. [1974] showed that mice chronically exposed to pulsed RFR initially showed a decrease and then an increase in susceptibility to the convulsant pentylenetetrazol. However, Pappas et al. [1983] showed no significant interaction effect of RFR on pentylenetetrazol-induced seizures nor the efficacy of chlordiazepoxide to block the seizure in rats. A more thorough study of the different parameters of RFR exposure on benzodiazepine receptors in the brain may explain these findings. Benzodiazepine receptors are very dynamic and can undergo rapid changes in properties in response to environmental stimuli [Braestrup et al., 1979; Lai and Carino, 1990b; Medina et al., 1983a,b; Soubrie et al., 1980; Weizman et al., 1989]. However, the direction of change and extent of effect depend on the stimulus and experimental conditions.

We conducted experiments to study the effect of acute RFR exposure on the actions of various psychoactive drugs [Lai et al., 1983; 1984a,b]. We found that acute (45 min) exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, whole body average SAR 0.6 W/kg) enhanced apomorphine-hypothermia and stereotypy, morphine-catalepsy, and pentobarbital-hypothermia and narcosis, but it attenuated amphetamine-hyperthermia and ethanol-hypothermia. These psychoactive drugs are lipid-soluble and readily enter the central nervous system and the effects observed are not unidirectional, i.e., depending on the drug studied, increase or decrease in action was observed after RFR exposure. Therefore, these effects cannot be explained as a change in entry of the drugs into the brain, e.g., change in blood-brain barrier permeability or alteration in drug metabolism as a result of RFR exposure. Our finding that acute low-level RFR attenuated ethanol-hypothermia in the rat was replicated by Hjeresen et al. [1988] at a lower whole body average SAR of 0.3 W/kg. Blood ethanol level measurements indicated that the effect was not due to changes in metabolism or disposition of ethanol in the body. Results from further experiments [Hjeresen et al., 1989] suggested that the β-adrenergic mechanism in the brain might be involved in the attenuation effect of RFR on ethanol-induced hypothermia in the rat.

We further found that the effects of RFR on amphetamine-hyperthermia [Lai et al., 1986b] and ethanol-hypothermia could be classically conditioned to cues in the exposure environment after repeated exposure. Another interesting finding in our research was that some of the effects of RFR on the actions of the psychoactive drugs could be blocked by pretreating the rats with narcotic antagonists before exposure, suggesting the involvement of endogenous opioids [Lai et al., 1986b]. The hypothesis that low-level RFR activates endogenous opioids in the brain was further supported by an experiment showing that the withdrawal syndromes in morphine-dependent rats could be attenuated by RFR exposure [Lai et al., 1986a]. This hypothesis can explain most of the RFR-psychoactive drug interaction effects reported in our studies [see Table I in Lai et al., 1987a].

In another study [Lai et al., 1984b], water-deprived rats were allowed to drink a 10% sucrose solution from a bottle in the waveguide. Exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.6 W/kg) did not significantly affect the consumption of the sucrose solution. However, when the sucrose solution was substituted by a 10% sucrose-15% ethanol solution, the rats drank ~25% more when they were exposed to the RFR than when they were sham exposed. The hypothesis that RFR activates endogenous opioids in the brain can also explain the increased ethanol consumption during RFR exposure. Recent studies have shown that activation of opioid mechanisms in the central nervous system can induce voluntary ethanol drinking in the rat [Nichols et al., 1991; Reid et al., 1991; Wild and Reid, 1990].

Frey and Wesler [1983] studied the effect of low-level RFR (1200 MHz, pulsed, 0.2 mW/cm^2, 15 min) on central dopaminergic functions. Radiofrequency radiation was found to attenuate the effect to both a high dose (1 mg/kg, IP) and a low dose (0.1 mg/kg, IP) of apomorphine on the latency of the tail-flick responses in the rat. The tail-flick test is a measure of pain perception in animals. These data are difficult to explain, since high dose and low dose of apomorphine affect predominantly the post- and presynaptic-dopamine receptors, respectively. These two types of dopamine receptors have opposite effects on dopamine transmission and functions. Other experiments indicating an effect of RFR on dopamine function in the brain are those of Michaelson et al. [1961] and Jauchem et al. [1983, 1985] showing the effect of chlorpromazine on RFR-induced hyperthermia, and our experiment showing an enhancement of apomorphine-hypothermia by RFR [Lai et al., 1983]. Chlorpromazine and apomorphine are dopamine antagonist and agonist, respectively. On the other hand, Thomas et al. [1980] reported no significant interaction effect between chlorpromazine and pulsed RFR (2800 MHz, 2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.2 W/kg) on rats responding on a fixed interval reinforcement schedule for food reward. However, Thomas and Maitland [1979] reported that exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.2 W/kg) potentiated the effect of d-amphetamine on rats responding on a DRL-schedule of reinforcement. Amphetamine is an agonist of both dopamine and norepinephrine functions in the brain.

Two studies imply RFR affects serotonergic activity in the brain. Galloway and Waxler [1977] reported interaction between RFR and a serotonergic drug. Rhesus monkeys trained on a color-matching task were irradiated with continuous-wave 2450-MHz RFR at different dose rates. The animals were also treated with the serotonergic drug fenfluramine, which inhibits granule reuptake and storage of serotonin in nerve terminals and causes a long-lasting depletion of serotonin in the brain. Radiofrequency radiation alone had no significant effect on performance, whereas fenfluramine alone decreased the response accuracy and response rate in performing the task. Exposure to RFR plus the drug treatment produced a synergistic effect. A severe disruption of responding was observed. The authors speculated that RFR may act like fenfluramine, i.e., decreases serotonergic functions in the brain. This may be related to the finding of Frey [1977] who reported that RFR exposure decreased tail pinch- induced aggressive behavior in the rat. Fenfluramine and other drug treatments that decrease serotonergic functions in the brain were shown to suppress aggressive behavior elicited by electric foot-shock in rats [Panksepp et al., 1973].

Results from one of our experiments also indicated an increase in serotonergic activity in the brain of rats exposed to RFR. We [Lai et al., 1984c] observed an increase in body temperature (~1.0 ^{o}C) in the rat after acute (45 min) exposure to pulsed 2450-MHz RFR (2 μs pulses, 500 pps, 1 mW/cm^2, SAR 0.6 W/kg). This hyperthermic effect was blocked by pretreating the rats before exposure with the serotonin antagonists, cinanserin, cyproheptadine, and metergoline, but not by the peripheral serotonin antagonist, xylamidine, implying that the effect is mediated by serotonergic mechanism inside the central nervous system.

The findings that RFR can affect (potentiate or attenuate) the actions of psychoactive drugs could have important implication in considering the possible hazardous effects of the radiation. Most of the drugs studied, such as the benzodiazepines and neuroleptics, are widely used for therapeutic purposes. On the other hand, drugs can enhance the biological effects of RFR. Example are the studies of Kues and Monahan [1992] and Kues et al. [1990; 1992] showing synergistic effects of drugs on corneal endothelium damages and retinal degeneration in the monkey induced by repeated exposure to RFR. They found that application of the drugs timolol and pilocarpine to the eye before RFR exposure could lower the threshold of the RFR effect by 10 folds (from 10 to 1 mW/cm^2). Timolol and pilocarpine are commonly used in the treatment of glaucoma.

PSYCHOLOGICAL EFFECTS OF RADIOFREQUENCY RADIATION

A necessary consequence of change in neurological activity is a change in behavior. If RFR alters electrophysiological and neurochemical functions of the nervous system, changes in behavior will result. Effects of RFR on both spontaneous and learned behaviors have been investigated.

Spontaneous Behaviors

The effects of RFR on motor activity were the subjects of various studies. Changes in motor activity are generally regarded as indications of changes in the arousal state of an animal. Hunt et al. [1975] reported increased motor activity in rats after 30 min of exposure to 2450-MHz RFR (SAR of 6.3 W/kg) and decreased swimming speed in cold (24 ^{o}C) water. However, Roberti [1975] reported no significant change in locomotor activity in rats after long term (185-408 h) exposure to RFR at different frequencies and intensities (SARs 0.15-83 W/kg). Modak et al. [1981] reported a decrease in motor activity in rats exposed to a single pulse (15 or 25 ms) of 2450-MHz RFR, which increased the brain temperature by 2-4 ^{o}C.

Mitchell et al. [1977] reported an increase in motor activity on a small platform of rats exposed to 2450-MHz RFR (average SAR 2.3 W/kg, 5 hr/day, 5 days/week for 22 weeks). Motor activity of the RFR exposed rats increased during the first week of exposure and stayed higher than controls throughout the period of the experiment. Moe et al. [1976] reported a decrease in motor activity of rats exposed to RFR (918 MHz, SARs 3.6-4.2 W/kg) during the dark period of the light-dark cycle in a chronic exposure experiment (10 h/night for 3 weeks). Lovely et al. [1977] repeated the experiment using a lower intensity (2.5 mW/cm^2, SARs 0.9-1.0 W/kg, 10 h/night, 13 weeks) and found no significant change in motor activity in the exposed rats. Frey [1977] subjected rats to 1300-MHz pulsed RFR (0.5 ms pulses, 1000 pps, average power density of 0.65 or 0.2 mW/cm^2, peak power densities 1.3 and 0.4 mW/cm^2). He reported a decrease in tail pinch-induced aggressive behavior in RFR-exposed rats. Increased latency, decrease in duration, and episodes of fighting after tail pinching were observed between two rats being irradiated with RFR. Decrease in motor coordination on a motor-rod was also reported in pulsed RFR-exposed (1300 and 1500 MHz, 0.5 ms pulses, 1000 pps) rats. The effect occurred at peak power densities between 0.4 and 2.8 mW/cm^2.

Rudnev et al. [1978] studied the behavior of rats exposed to 2375-MHz RFR at 0.5 mW/cm^2 (SAR 0.1 W/kg), 7 h/day for 1 month. They reported decreases in food intake, balancing time in a treadmill and inclined rod, and motor activity in an open-field after 20 days of exposure. Interestingly, the open-field activity was found to be increased even at 3 months postexposure. In a long-term exposure study [Johnson et al., 1983], rats were exposed to pulsed 2450-MHz RFR (10 μs pulses, 800 pps) from 8 weeks to 25 months of age (22 h/day). The average whole body SAR varied as the weight of the rats increased and was between 0.4-0.15 W/kg. Open field activity was measured in 3-min sessions with an electronic open-field apparatus once every 6 weeks during the first 15 months and at 12 week intervals in the final 10 weeks of exposure. They reported a significantly lower open field activity only at the first test session and a rise in the blood corticosterone level was also observed at that time. The authors speculated that RFR might be minimally stressful to the rats.

D'Andrea et al. [1979, 1980] reported decreased motor activity on a stabilimetric platform and no significant change in running wheel activity measured overnight in rats exposed to 2450-MHz RFR (5 mW/cm^2, SAR 1.2 W/kg). However, an increase in both measurements was observed in rats exposed to 915-MHz RFR (5 mW/cm^2, SAR 2.5 W/kg). These changes in locomotor activity could be due to the thermal effect of RFR.

In a more recent experiment, Mitchell et al. [1988] studied several behavioral responses in rats after 7 h of exposure to continuous-wave 2450-MHz RFR (10 mW/cm^2, average SAR 2.7 W/kg). Decreases in motor activity and responsiveness (startle) to loud noise (8 kHz, 100 dB) were observed immediately after exposure. The rats were then trained to perform a passive avoidance task and tested for retention of the learning one week later. There was no significant difference in retention between the RFR-exposed and sham-exposed animals. The authors concluded that RFR altered responsiveness to novel environmental stimuli in the rat.

Two studies investigated the effects of pre- and postnatal-RFR on behavior. Kaplan et al. [1982] exposed groups of pregnant squirrel monkeys starting at the second trimester of pregnancy to 2450-MHz RFR at SARs of 0, 0.034, 0.34, and 3.4 W/kg (3 h/day, 5 days/week). The motor activity of the monkeys was observed at different times during the third trimester. No significant difference was observed among the different exposure groups. After birth, some dams and neonates were exposed for 6 months at the same prenatal conditions and then the offspring were exposed for another 6 months. Behavior of the mothers and offspring was observed and scored each week for the first 24 weeks postpartum. The authors observed no significant difference in maternal behavior or the general activity of the offspring among the different exposure groups. Visual-evoked EEG changes in the occipital region of the skull of the offspring were also studied at 6, 9, and 12 months of age. No significant effect of perinatal RFR-exposure was reported.

In another study [Galvin et al., 1986], rats were exposed to 2450-MHz RFR (10 mW/cm^2, 3 h/day) either prenatally (days 5-20 of gestation, whole body SAR estimated to be 2-4 W/kg) or perinatally (prenatally and on days 2-20 postnatally, whole body SARs 16.5-5.5 W/kg). Several behaviors including motor behavior, startle to acoustic and air-puff stimuli, fore- and hind-limb grip strength, negative geotaxis, reaction to thermal stimulation, and swimming endurance were studied in the rats at various times postnatally. They reported a decrease in swimming endurance (time remaining afloat in 20 ^{o}C water with a weight clipped to the tail) in 30-day old perinatally-exposed rats. The air-puff startle response was enhanced in magnitude in the prenatally exposed rats at 30 days, but decreased at 100 days of age. The authors concluded that perinatal exposure to RFR altered the endurance and gross motor activity in the rat. It would be interesting to study the neurochemistry or brain morphology of these animals. As described in a previous section, Albert et al. [1981a,b] and Albert and Sherif [1988] observed morphological changes in the cerebellum of rats subjected to RFR exposure perinatally at lower SAR (2-3 W/kg). It is well known that interference of cerebellar maturation can affect an animal's motor development [Altman, 1975].

O'Connor [1988] exposed pregnant rats to continuous-wave 2450-MHz (27-30 mW/cm^2) RFR between day 1 to day 18 or 19 of gestation (6 h/day). Their offspring were studied at different ages. She reported no significant effect of prenatal RFR exposure on visual cliff test, open field behavior, climbing behavior on an inclined plane, and avoidance behavior in a shuttlebox. The exposed animals showed altered sensitivity to thermally related tests evidenced by preference for the cooler section of a temperature-gradient alley way, longer latency to develop thermally induced seizure, and formed smaller huddle groups at 5 days of age.

Learned Behaviors

Many studies have investigated the effect of RFR exposure on learned behavior. King et al. [1971] used RFR as the cue in a conditioned suppression experiment. In conditioned suppression an animal is first trained to elicit a certain response (e.g., bar-press for food). Once a steady rate of response is attained, a stimulus (e.g., a tone) will signify the on-coming of a negative reinforcement (e.g., electric foot shock). The animal will soon learn the significance of the stimulus and a decrease in responding (conditioned suppression) will occur after the presentation of the stimulus. In the experiment of King et al. [1971], rats were trained to respond at a fixed-ratio schedule for sugar water reward. In a 2-h session, either a tone or RFR would be presented and occasionally followed by an electric foot shock. Radiofrequency radiation of 2450 MHz, modulated at 12 and 60 Hz and at SARs of 0.6, 1.2, 2.4, 4.8, and 6.4 W/kg were used as the conditioned stimulus. With training, consistent conditioned suppression was observed with RFR at 2.4 W/kg and higher.

Several studies used RFR as a noxious stimulus, i.e., a negative reinforcer, to induce or maintain conditioned behavior. In an earlier paper, Monahan and Ho [1976] speculated that mice exposed to RFR tended to change their body orientation in order to reduce the SAR in the body, suggesting that they were avoiding the radiation. To support the point that RFR is a noxious stimulus, Monahan and Henton [1977b] demonstrated that mice can be trained to elicit an operant response in order to escape or avoid RFR (2450-MHz, 40 W/kg).

In a series of experiments, Frey and his associates [Frey and Feld, 1975; Frey et al., 1975] demonstrated that rats spent less time in the unshielded compartment of a shuttlebox, when the box was exposed to 1200-MHz pulsed RFR (0.5 μs pulses, 1000 pps, average power density 0.2 mW/cm^2, peak power density 2.1 mW/cm^2) than during sham exposure. When a continuous-wave RFR (1200-MHz, 2.4 mW/cm^2) was used, rats showed no significant preference to remain in the shielded or unshielded side of the box. The authors also reported that rats exposed to the pulsed RFR were more active. Hjeresen et al. [1979] replicated this finding using pulsed 2880-MHz RFR (2.3 μs pulses, 100 pps, average power density 9.5 mW/cm^2) and showed that the preference to remain in the shielded side of a shuttlebox during RFR exposure could be generalized to a 37.5-kHz tone. Masking the radiation-induced auditory effect with a 10-20 kHz noise also prevented the development of shuttlebox-side preference during pulsed RFR exposure. These data suggest that the pulsed RFR-induced side preference is due to the auditory effect. In the studies of Frey et al. [1975] and Hjeresen et al. [1979] increase in motor activity was also reported when the animals were exposed to the pulsed RFR. Interestingly, this pulsed RFR-induced increase in motor activity was not affected by noise masking. Thus, the RFR avoidance and enhancement in motor activity by pulsed RFR may involve different neural mechanisms. Related to the above experiments is that the auditory effect of pulsed RFR can be used as a cue to modify an animal's behavior. Johnson et al. [1976] trained rats to respond (making nose pokes) on a fixed ratio reinforcement schedule for food pellets in the presence of a tone (7.5 kHz, 10 pps, 3 μs pulses). Reinforced period was alternated with periods of no reward when no tone was presented. Rats, after learning this response, responded when the tone was replaced by pulsed RFR (918 MHz, 10 μs pulses, 10 pps, energy per pulse 150 μJ/cm^2) during both reinforced and unrewarded periods. Apparently, the response to the tone had generalized to the pulsed RFR.

In another experiment, Carroll et al. [1980] showed that rats did not learn to go to a 'safe' area in the exposure cage in order to avoid exposure to RFR (918-MHz, pulse modulated at 60 Hz, SAR 60 W/kg), whereas the animals learned readily to escape from electric foot shock by going to the 'safe' area. In a further study, Levinson et al. [1982] showed that rats could learn to enter a 'safe' area, when the RFR (918-MHz, 60 W/kg) was paired with a light stimulus. Entering the area would turn off both the radiation and light. They also showed that rats could learn to escape by entering the 'safe' area when RFR was presented alone, but learned at a lower rate than when the RFR was paired with the light.

Several studies investigated the effect of RFR on conditioned taste aversion. It was discovered that consumption of food or drink of novel taste followed by a treatment which produced illness, e.g., X-irradiation or poison, an animal will learn to associate the taste with the illness and will later avoid the food or drink. Different from the traditional conditioning process, where conditioning occurs only when the response is followed immediately by the reinforcement, taste aversion conditioning can occur even if the illness is induced 12 h after the taste experience. Another characteristic of conditioned taste aversion is that the conditioning is very selective. An animal can learn to associate the taste with the illness, but not the place where the food or drink was taken, i.e., it will avoid the taste, but not the place where the food or drink was consumed. This phenomenon is known as 'belongingness', i.e., association (conditioning) between some stimulus pairs is easier than others [Garcia and Koelling, 1966; Garcia et al., 1966]. Thus, RFR has to produce the 'proper' type of adverse effect in the animal in order for conditioned taste aversion to occur.

Monahan and Henton [1977a] irradiated rats for 15 min with 915-MHz RFR of various intensities (up to a SAR of ~17 W/kg) after 15 min of access to 10% sucrose solution as a substitute for the normal drinking water. When the animals were offered the sucrose solution 24 h later, no conditioned taste aversion was observed. They drank the same amount of sucrose solution as the previous day. Conditioned taste aversion was also studied by Moe et al. [1976] and Lovely et al. [1977] in experiments of similar design in which rats were exposed chronically to 918-MHz RFR at 10 mW/cm^2 (SAR 3.9 W/kg) and 2.5 mW/cm^2 (SAR 1.0 W/kg), respectively. Rats were provided with 0.1% saccharin drinking solution during the whole period of exposure in the Moe et al. [1976] study and between the 9th to 13th week of exposure in the Lovely et al. [1977] study. They observed no significant difference in the consumption of saccharin solution, nor a preference for either water or saccharin solution between the RFR-exposed and sham-exposed animals. Thus, no taste aversion developed. Perhaps, RFR does not produce an intensive sickness or the proper type of 'belongingless' for the conditioning to occur. However, in another study, Lovely and Guy [1975] reported that rats that were exposed to continuous-wave 918-MHz RFR for 10 min at >25 mW/cm^2 (SAR ~22.5 W/kg) and then allowed to drink saccharin solution, showed a significant reduction in saccharin consumption when tested 24 h later. No significant effect was found in rats exposed to RFR at 5 or 20 mW/cm^2.

In addition to using RFR as an aversive stimulus, it has also been used as a positive reinforcer. Marr et al. [1988] reported that rhesus monkeys could be trained to press a lever on a fixed ratio schedule to obtain 2 sec-pulses of RFR (6500 MHz, 50 mW/cm^2, estimated SAR 12 W/kg) when the monkeys were placed in a cold environment (0 ^{o}C).

A study by Bermant et al. [1979] investigated the thermal effect of RFR using the classical conditioning paradigm. They reported that after repeated pairing of a 30 sec tone with RFR (2450 MHz, 10 sec at SAR 420 W/kg or 30 sec at SAR 220 W/kg), the tone when presented alone could elicit a conditioned hyperthermia from the rat. An effect which may be relevant to the finding of this experiment is that drug-induced changes in body temperature (hyperthermia or hypothermia) in animals can also be classically conditioned [Cunningham et al., 1984].

We have conducted experiments to investigate whether the effects of low-level RFR on psychoactive drug actions and central cholinergic activity can be classically conditioned to cues in the exposure environment. Classical conditioning of drug effects with environmental cues as the conditioned stimulus have been reported and such conditioned responses have been suggested to play a role in drug response, abuse, tolerance, and withdrawal [Le et al., 1979; Siegel, 1977, Siegel et al., 1982, Wikler, 1973a; Woods et al., 1969]. We found that the effects of RFR on amphetamine-induced hyperthermia and cholinergic activity in the brain can be classically conditioned to environmental cues [Lai et al., 1986b, 1987c].

In earlier experiments, we reported that acute (45 min) exposure to 2450-MHz RFR at average whole body SAR of 0.6 W/kg attenuated amphetamine-induced hyperthermia [Lai et al., 1983] and decreased HACU in the frontal cortex and hippocampus [Lai et al., 1987b] in the rat. In the conditioning experiments, rats were exposed to 2450-MHz pulsed RFR (2 µs pulses, 500 pps, 1.0 mW/cm^2, SAR 0.6 W/kg) in ten daily 45-min sessions. On day 11, animals were sham-exposed for 45 min and either amphetamine-induced hyperthermia or high-affinity choline uptake (HACU) in the frontal cortex and hippocampus was studied immediately after exposure. In this paradigm the RFR was the unconditioned stimulus and cues in the exposure environment were the neutral stimuli, which after repeated pairing with the unconditioned stimulus became the conditioned stimulus. Thus on the 11th day when the animals were sham-exposed, the conditioned stimulus (cues in the environment) alone would elicit a conditioned response in the animals. In the case of amphetamine-induced hyperthermia [Lai et al., 1986b], we observed a potentiation of the hyperthermia in the rats after the sham exposure. Thus, the conditioned response (potentiation) was opposite to the unconditioned response (attenuation) to RFR. This is known as 'paradoxical conditioning' and is seen in many instances of classical conditioning [cf. Mackintosh, 1974]. In addition, we found in the same experiment that, similar to the unconditioned response, the conditioned response could be blocked by the drug naloxone, implying the involvement of endogenous opioids. In the case of RFR-induced changes in cholinergic activity in the brain, we [Lai et al., 1987c] found that conditioned effects also occurred in the brain of the rat after the session of sham exposure on day 11. An increase in HACU in the hippocampus (paradoxical conditioning) and a decrease in the frontal cortex were observed. In addition, we found that the effect of RFR on hippocampal HACU habituated after 10 sessions of exposure, i.e., no significant change in HACU in the hippocampus was observed in animals exposed to the RFR on day 11. On the other hand, the effect of RFR on frontal cortical HACU did not habituate after the repeated exposure.

An explanation for the paradoxical conditioning phenomenon was given by Wikler [1973b] and Eikelboom and Stewart [1982]. The direction of the conditioned response (same as or opposite to the unconditioned response) depends on the site of action of the unconditioned stimulus, whether it is on the afferent or efferent side of the affected neural feedback system. Thus, in order to further understand the neural mechanisms of the conditioned effects, the site of action of RFR on the central nervous system has to be identified.

Little work has been done to investigate the effects of RFR on memory functions. We [Lai et al., 1989b] studied the effect of acute (20 or 45 min) RFR exposure (2450-MHz, 1 mW/cm^2, SAR 0.6W/kg) on the rats' performance in a radial-arm maze, which measures spatial learning and memory functions. The maze consists of a central circular hub with arms radiating out like the spokes of a wheel. In this task, food-deprived animals are trained to explore the arms of the maze to obtain food reinforcement at the end of each arm. In each session they have to enter each arm once and a reentry is considered as an error. This task requires the so called 'working memory', i.e., the rat has to remember the arms it has already entered during the course of a session. Working memory requires the functions of the cholinergic innervations in the frontal cortex and hippocampus [Dekker et al., 1991; Levin, 1988]. Both have been shown to be affected by acute RFR exposure [Lai et al., 1987b]. We [Lai et al., 1989b] found that acute (45 min) exposure to RFR before each session of maze running significantly retarded the rats' abilities to perform in the maze. They made significantly more errors than the sham-exposed rats. This result agrees with the neurochemical finding that 45 min of RFR exposure decreased the activity of the cholinergic systems in the frontal cortex and hippocampus of the rats [Lai et al., 1987b]. However, 20 min of RFR exposure, which increased cholinergic activity in the brain, did not significantly affect maze performance. Apparently, increase in cholinergic activity cannot further improve the performance, since the neural systems involved in the memory function may be working at optimal levels under normal conditions. In a recent experiment [Lai et al., 1993], we have shown that the microwave-induced working memory deficit in the radial-arm maze was reversed by pretreating the rats before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter sysatems inside the central nervous system are involved in the microwave-induced spatial memory deficit.

Several studies have investigated the effect of RFR on discrimination learning and responding. Hunt et al. [1975] trained rats to bar press for saccharin water rewards in the presence (5 sec duration) of a flashing light and not to respond in the presence of a tone (unrewarded). After 30 min of exposure to 2450-MHz RFR, modulated at 20 Hz and at SAR of 6.5 or 11.0 W/kg, rats made more misses at the presence of the light, but there were no significant changes in the incidences of bar-pressing errors when the tone was on. The effect was more prominent at the higher dose rate. Galloway [1975] trained rhesus monkeys on two behavioral tasks to obtain food reward. One was a discrimination task in which the monkey had to respond appropriately depending on which of the two stimuli was presented. The other task was a repeated acquisition task in which a new sequence of responses had to be learned everyday. After training, the animals were irradiated with continuous-wave 2450-MHz RFR applied to the head prior to each subsequent behavioral session. The integral dose rates varied from 5-25 W. Some of these dose rates caused convulsions in the monkeys. The radiation was shown to exert no significant effect on the discrimination task, whereas a dose-dependent deficit in performance was observed in the repeated acquisition task. Cunitz et al., [1979] trained two rhesus monkeys to move a lever in different directions depending on the lighting conditions in the exposure cage in order to obtain food reinforcement on a fixed ratio schedule. After the animals' performance had reached a steady and consistent level, they were irradiated at the head with continuous-wave 383-MHz RFR at different intensities in subsequent sessions. Radiation started 60 min before and during a session of responding. The authors reported a decrease in the rate of correct responding when the SAR at the head reached 22-23 W/kg. In another study, Scholl and Allen [1979] exposed rhesus monkeys to continuous-wave 1200-MHz RFR at SARs of 0.8-1.6 W/kg and observed no significant effect of the radiation on a visual tracking task.

de Lorge [1976] trained rhesus moneys on an auditory vigilance (observing-response) task. The task required continuous sensory-motor activities in which the monkeys had to coordinate their motor responses according to the stimulus cues presented. In the task the monkeys had to press the right lever that produced either a 1070-Hz tone for 0.5 sec or a 2740-Hz tone. The 1070-Hz tone signalled an unrewarded situation. Pressing a left lever when the 2740-Hz tone was on would produce a food reward. Presentation of the higher frequency tone was on a variable interval schedule. After the monkeys had learned to perform the task at a steady level, they were irradiated with 2450-MHz RFR of different intensities. Decreased performance and increased latency time in pressing the left lever were observed when the power density at the head was at 72 mW/cm^2. The deficits could be due to an increase in colonic temperature after exposure to the high intensity RFR.

de Lorge [1979] trained squirrel monkeys to respond to another observing-response task using visual cues. After learning the task, the animals were exposed to 2450-MHz RFR (sinusoidally modulated at 120 Hz) for 30 or 60 min at different power densities (10-75 mW/cm^2) in subsequent sessions. Their performances were disrupted at power densities >50 mW/cm^2. The disruption was power density-dependent and occurred when the rectal temperatures increased more than 1 ^{o}C. In a more recent experiment, de Lorge [1984] studied rhesus monkeys trained on the auditory vigilance task and the effects of exposure to RFRs of different frequencies (225, 1300, and 5800 MHz). Reduction in performance was observed at different power density thresholds for the frequencies studied: 8.1 mW/cm^2 (SAR 3.2 W/kg) for 225 MHz, 57 mW/cm^2 (SAR 7.4 W/kg) for 1300 MHz, and 140 mW/cm^2 (SAR 4.3 W/kg) for 5800 MHz. de Lorge concluded that the behavioral disruption under different frequencies of exposure was more correlated with change in body temperature. Disruption occurred when the colonic temperature of the animal had increased by 1 ^{o}C.

Many studies have investigated the effects of RFR on reinforcement schedule-controlled behavior. Sanza and de Lorge [1977] trained rats on a fixed interval schedule for food pellets. After 60 min of exposure to 2450-MHz RFR (modulated at 120 Hz) at 37.5 mW/cm^2, a decrease in response with an abrupt onset was observed. This effect was more pronounced in rats with a high base line of response rate on the fixed interval schedule. No significant effect on response was observed at power densities of 8.8 and 18.4 mW/cm^2.

D'Andrea et al. [1976] trained rats to bar-press for food at a variable interval schedule. After a constant responding rate was attained, the animals were irradiated with continuous- wave RFRs of 360, 480, or 500 MHz. Bar-press rates were decreased only when the rats were exposed to the 500-MHz radiation at a SAR of approximately 10 W/kg. The animals also showed significant signs of heat stress. In a subsequent study [D'Andrea et al., 1977] RFRs of different frequencies and intensities were studied on their effect on bar-pressing rate on a variable interval schedule. It was found that the latency time of stoppage to respond after the radiation was turned on correlated with the rate of rise in body temperature of the animal. These experiments definitely demonstrated the thermal effect of RFR on operant behavior.

Gage [1979a] trained rats on a variable interval schedule for food reinforcement. Different groups of rats were exposed overnight (15 h) to continuous-wave 2450-MHz RFR at either 5, 10, or 15 mW/cm^2. Responses were tested immediately after exposure. No significant difference in performance was found between the RFR- and sham-exposed rats when exposure was done at an ambient temperature of 22 ^{o}C. However, a power density- dependent reduction in response rate and increase in response duration was found in the RFR-exposed rats when the irradiation was carried out at 28 ^{o}C. At the higher ambient temperature, heat dissipation from the body was less efficient and the exposed rats had higher body temperatures postexposure.

Lebovitz [1980] also studied the effects of pulsed 1300-MHz (1 μs pulses, 600 pps) RFR on rats bar-pressing on a fixed interval schedule for food reinforcement. Both food reinforced bar presses and unrewarded bar presses during the intervals were studied. No significant effect was detected in both types of response at SAR of 1.5 W/kg. However, at 6 W/kg, there was a slight reduction in rewarded bar presses and a large reduction in unrewarded bar presses. The authors concluded that the unrewarded behavior was more susceptible to the effect of RFR than the rewarded behavior. Another related experiment was reported by Sagan and Medici [1979] in which water-deprived chicks were given access to water on fixed intervals irrespective of their responses. During the time between water presentations the chicks showed an increase in motor activity known as 'interim behavior'. Exposure to 450-MHz RFR amplitude-modulated at 3 and 16 Hz at power densities of either 1 or 5 mW/cm^2 during session had no significant effect on the 'interim behavior'.

Effects of RFR on complex operant response sequence and reinforcement schedules were studied in various experiments. de Lorge and Ezell [1980] tested rats on a vigilance behavioral task during exposure to pulsed 5620-MHz RFR and then to pulsed 1280-MHz RFR. In this task, rats had to discriminate two tones in order to press one of two bars appropriately for food reinforcement. Behavioral decrement was observed at an SAR of 2.5 W/kg with the 1280-MHz radiation, but at 4.9 W/kg with the 5620-MHz radiation. Gage [1979b] trained rats to alternate responses between 2 levers at 11-30 times for a food reinforcement. Decrement in response rates was observed after 15 h of exposure to continuous-wave 2450-MHz RFR at 10, 15, and 20 mW/cm^2 (0.3 W/kg per mW/cm^2).

Thomas et al. [1975] trained rats to bar press on two bars: a fixed ratio of 20 on the right bar (20 bar presses produced a food pellet reward) and differential reinforcement of low rate (DRL) on the left bar (bar presses had to be separated by at least 18 sec and no more than 24 sec to produce a reward). There was a time-out period between schedules, i.e., no reinforcement available for responding. Animals were tested 5-10 min after 30 min of exposure to either continuous-wave 2450-MHz, pulsed 2860-MHz (1 μs pulses, 500 pps) or pulsed 9600-MHz (1 μs pulses, 500 pps) RFR at various power densities. An increase in DRL response rate was observed with 2450-MHz radiation >7.5 mW/cm^2 (SAR 2.0 W/kg), 2860-MHz RFR >10 mW/cm^2 (2.7 W/kg), and 9600-MHz RFR >5 mW/cm^2 (SAR 1.5 W/kg). A decrease in the rate of response at the fixed ratio schedule was seen in all three frequencies when the power density was greater than 5 mW/cm^2. In addition, an increase in response rate was observed during time-out periods under irradiation of the three frequencies of RFR at greater than 5 mW/cm^2.

In another study, Thomas et al. [1976] trained rats to bar press on a tandem schedule using 2 bars. Pressing the right bar for at least 8 times before pressing the left bar would give a food pellet reward. A power density-dependent decrease in the percentage of making 8 or more consecutive responses on the right bar before pressing the left bar was observed in the animals after 30 min of exposure to pulsed 2450-MHz RFR (1 μs pulses, 500 pps) at power densities of 5, 10, and 15 mW/cm^2.

Schrot et al [1980] also trained rats to learn a new daily sequence of pressing of three bars for food reinforcement. An increased number of errors and decreased learning rates were observed in the animals after 30 min of exposure to pulsed 2800-MHz RFR (2 μs pulses, 500 pps) at average power densities of 5 and 10 mW/cm^2 (SARs 0.7 and 1.7 W/kg, respectively). No significant effect on performance was observed at power densities of 0.25, 0.5, and 1 mW/cm^2.

Several studies investigated the effects of chronic RFR exposure on schedule controlled-behavior. Mitchell et al. [1977] trained rats to respond on a mixed schedule of reinforcement

(FR-5 EXT-15 sec), in which 5 responses would give a reward and then a 15 sec lapse time (extinction period) was required before a new response would be rewarded. In addition, the schedule of reinforcement was effective when a lamp was on, while no reinforcement was given when the lamp was off. Rats were then exposed to 2450-MHz RFR (average SAR 2.3 W/kg) for 22 weeks (5 h/day, 5 days/week) and tested at different times during the exposure period. The RFR-exposed rats showed higher responses during the extinction period, indicating poorer discrimination of the response cues. In another also pretrained task, rats had to press a bar to postpone the onset of unsignalled electric foot-shocks (unsignalled avoidance paradigm). No significant difference in performance of this task was observed between the RFR- and sham-exposed animals.

Two series of well-designed experiments were run by D'Andrea et al. [1986a,b] to investigate the effects of chronic RFR exposure on behavior. In one experiment, rats were exposed for 14 weeks (7 h/day, 7 days/week) to continuous-wave 2450-MHz RFR at 2.5 mW/cm^2 (SAR 0.7 W/kg). Decrease in the threshold of electric foot shock detection (i.e., increase in sensitivity) was observed in the irradiated rats during the exposure period. Increased open-field exploratory behavior was observed in the rats at 30 days postexposure. After exposure, the rats were trained to bar press on an interresponse time criterion (IRT). In this schedule, the animals had to respond within 12 to 18 sec after the previous response in order to receive a food reward. Radiofrequency radiation exposed rats emitted more responses during the training period. When the training was completed, the RFR-exposed rats had lower efficiency in bar-pressing to obtain food pellets, i.e., they made more inappropriate responses and received fewer food pellets than the sham-exposed rats during a session. In a signalled two-way active avoidance shuttlebox test, the RFR-exposed rats showed less avoidance response than the sham-exposed rats during training; however, no significant difference in responses in the shuttlebox test was detected at 60 days after exposure between the RFR- and sham-exposed animals. In another series of experiments, rats were exposed to 2450-MHz RFR at 0.5 mW/cm^2 (SAR 0.14 W/kg) for 90 days (7 h/day, 7 days/week). Open-field behavior, shuttlebox performance, and IRT schedule-controlled bar-pressing behavior for food pellets were studied at the end of the exposure period. A small deficit in shuttlebox performance and increased rate of bar-pressing were observed in the RFR exposed rats. Summarizing the data from these two series of experiments [D'Andrea et al., 1986a,b], D'Andrea and his co-workers concluded that the threshold for the behavioral and physiological effects of chronic RFR exposure in the rats studied in their experiments occurred between the power densities of 0.5 mW/cm^2 (SAR 0.14 W/kg) and 2.5 mW/cm^2 (SAR 0.7 W/kg).

D'Andrea et al. [1989] recently studied the behavioral effects of high peak power RFR pulses of 1360-MHz. Rhesus monkeys performing on a complicated reinforcement-schedule involving time-related behavioral tasks (inter-response time, time discrimination, and fixed interval responses) were exposed to high peak power RFR (131.8 W/cm^2 rms, pulse repetition rate 2-32 Hz). No significant disturbance in performance was observed in the monkeys.

Akyel et al. [1991] also studied the effects of exposure to high peak power RFR pulses on behavior. In their experiment, rats pretrained to bar-press for food reinforcement on either fixed ratio, variable interval, or DRL schedule were exposed for 10 min to 1250-MHz pulses. Each pulse (10 µs width) generated a whole body specific absorption of 2.1 J/kg, which corresponds to a whole body average SAR of 0.21 mW/kg. The pulse rate was adjusted to produce different total doses (0.5-14 kJ/kg). Only at the highest dose (14 kJ/kg), stoppage of responding was observed after exposure, when the colonic temperature was increased by ~2.5 ^{o}C. Responding resumed when colonic temperature returned to within 1.1 ^{o}C above the preexposure level. When responding resumed, the response rates on the fixed ratio and variable interval schedules were below the preexposure base line level. Responses on the DRL schedule were too variable to allow a conclusion to be drawn. The authors concluded that the effect of the high peak power RFR pulses on schedule-controlled behavior was due to hyperthermia.

Behavior conditioning using different reinforcement schedules generates stable base line responses with reproducible patterns and rates. The behavior can be maintained over a long period of time (hrs) and across different experimental sessions. Thus, schedule-controlled behavior provides a powerful means for the study of RFR-behavior interaction in animals. On the other hand, the behavior involves complex stimulus-response interactions. It is difficult to conclude from the effects of RFR on schedule-controlled behavior the underlying neural mechanisms involved.

In a sense, these studies of RFR are similar to those of psychoactive drugs. A large volume of literature is available on the latter topic. A review of the literature on the effects of psychoactive drugs on schedule-controlled behavior reveals the complexity of the interaction and the limitation in data interpretation. In general, the effects of psychoactive drugs on schedule-controlled behavior is dose-dependent. In many cases, especially in behavior maintained by positive reinforcement, an inverted-U-function has been reported, i.e., the behavior is increased at low doses and decreased at high doses of the drug. In addition, the way that a certain drug affects schedule-controlled behavior depends on three main factors: (a) the base line level and pattern of responding of the animal: a general rule is that drugs tend to decrease the rate when the base line responding rate is high and vice versa. This is known as rate-dependency and is true with psychomotor stimulants, major and minor tranquilizers, sedative-hypnotics, and narcotics; (b) the schedule of reinforcement: in addition to its effect on the base line responding rate, a reinforcement schedule can have other specific effects on responses. For example, amphetamine has different effects on responses maintained on DRL schedule and punishment-suppressed responding schedule, even though both schedules generate a similar low response rate; and (c) the stimulus-control involved in the study: e.g., responses maintained by electric shock are more resistant to drug effects than responses maintained by positive reinforcers. On the other hand, some drugs have differential effects on signalled-avoidance versus continuous avoidance responding.

Thus, to fully understand the effect of RFR, the parameters of the radiation (different dose rates, frequency, duration of exposure, etc.), different reinforcement-schedules, and conditioning procedures have to be carefully studied and considered. However, there is evidence that the above determining factors on schedule-controlled behavior may also hold in the case of RFR. Exposure to RFR caused a decrease in response rate when a variable interval schedule that produces a steady rate of responding was used [D'Andrea et al., 1976; 1977; Gage, 1979a], and an increase in responding when the DRL-schedule of reinforcement was used [Thomas et al., 1975]. This may reflect the rate-dependency effect. On the other hand, stimulus control as a determinant of response outcome was seen in the study of Lebovitz [1980] when unrewarded responses were disrupted more by RFR than rewarded responses, and the study of Hunt et al. [1975] that showed the reverse relationship. In the former experiment a fixed interval schedule was used, whereas in the latter a discrimination paradigm was studied.

Another related point is that most psychoactive drugs affect body temperature. Stimulants cause hyperthermia, barbiturates cause hypothermia, and narcotics have a biphasic effect on body temperature (hyperthermia at low doses and hypothermia at high doses). It is not uncommon to observe a change of 2-3 ^{o}C within 30 min after a drug is administered. However, in reviewing the literature, there is no general correlation between the effects of the drugs on body temperature and schedule-controlled behavior. Thus, body temperature may not be an important factor in an animal's responding under schedule-controlled behavior, at least in the case of psychoactive drugs. On the contrary, some of the experiments described above strongly suggest the role of hyperthermia on the RFR effect on the behavior. Perhaps, a sudden and large increase in body temperature as in the case of RFR can have a major effect on responding.

Generally speaking, when effects were observed, RFR disrupted operant behavior in animals such as in the cases of discrimination responding [de Lorge and Ezell, 1980; Hunt et al., 1975; Mitchell et al., 1977], learning [Lai, 1989b; Schrot et al., 1980], and avoidance [D'Andrea et al., 1986a,b]. This is especially true when the task involved complex schedules and response sequence. In no case has an improvement in operant behavior been reported after RFR exposure. It is interesting that only disruptions in behavior by RFR exposure are reported. In the studies on EEG, both excitation (desynchronization) and depression (synchronization) have been reported after exposure to RFR [Bawin et al., 1979; Chizhenkova, 1988; Chou et al., 1982b; Dumansky and Shandala, 1976; Goldstein and Sisko, 1974; Dumansky and Shandala, 1976; Takeshima et al., 1979]. Motor activity has also been reported to increase [D'Andrea et al., 1979, 1980; Hunt et al., 1975; Mitchell et al., 1977; Rudnev et al., 1978] and decrease [Johnson et al., 1983; Mitchell et al., 1988; Moe et al., 1976; Rudnev et al., 1978] after RFR exposure. If these measurements can be considered as indications of electrophysiological and behavioral arousal and depression, improvement in operant behavior should occur under certain conditions of RFR exposure. This is especially true with avoidance behavior. Psychomotor stimulants that cause EEG desynchronization and motor activation improve avoidance behavior, whereas tranquilizers that have opposite effects on EEG and motor activity decrease avoidance behavior.

GENERAL DISCUSSION

After reviewing the studies on the effects of RFR on the central nervous system, one obvious question comes to my mind: "What is the mechanism responsible for the effects reported?" In most cases, especially the in vivo studies in which high intensities of irradiation were used resulting in an increase in body temperature, thermal effect is most likely the answer. Even in cases when no significant change in body temperature was detected, thermal effect cannot be excluded. An animal can maintain its body temperature by actively dissipating the heat load from the radiation. Activation of thermoregulatory mechanisms can lead to neuro-chemical, physiological, and behavioral changes. Temperature can be better controlled during in vitro studies. Uneven heating of the sample can still generate temperature gradients, which may affect the normal responses of the specimen studied. However, several points raised by some experiments suggest that the answer is not a simple one. They are: (a) 'Heating controls' do not produce the same effect of RFR [D'Inzeo et al., 1988; Seaman and Wachtel, 1978; Synder, 1971; Johnson and Guy, 1971; Wachtel et al., 1975]; (b) Window effects are reported [Bawin et al., 1975, 1979; Blackman et al., 1979, 1980a,b, 1989; Chang et al., 1982; Dutta et al., 1984, 1989, 1992; Lin-Liu and Adey, l982; Oscar and Hawkins, 1977; Sheppard et al., 1979]; (c) Modulated or pulsed RFR is more effective in causing an effect or elicits a different effect when compared with continuous-wave radiation of the same frequency [Arber and Lin, 1985; Baranski, 1972; Frey et al., 1973, 1975; Oscar and Hawkins, 1977; Sanders et al., 1983]; (d) Different frequencies of RFR produce different effects [D'Andrea et al., 1979, 1985; de Lorge and Ezell, 1980; Sanders et al., 1984; Thomas et al., 1975]; and (e) Different exposure orientations or systems of exposure produce different effects at the same average whole body SAR [Lai et al., 1984a, 1988].

I think most of these effects can be explained by the following factors:

1. The physical properties of RFR absorption in the body and the mechanisms by which RFR affects biological functions were not fully understood. In addition, use of different exposure conditions make it difficult to compare the results from different experiments.

2. Characteristics of the response system, i.e., the dependent variable, were not fully understood. In many cases, the underlying mechanism of the response system studied was not known.

3. Dose-response relationship was not established in many instances and conclusions were drawn from a single RFR intensity or exposure duration.

It is well known that the distribution of RFR in an exposed object depends on many factors such as frequency, orientation of exposure, dielectric constant of the tissue, etc. D'Andrea et al. [1987] and McRee and Davis [1984] pointed out the uneven distribution of energy absorbed in the body of an exposed animal with the existence of 'hot spots'. In experiments studying the central nervous system, Williams et al. [1984d] also reported a temperature gradient in the brain of rats exposed to RFR. Structures located in the center of the brain, such as the hypothalamus and medulla, had higher temperatures than peripheral locations, such as the cerebral cortex. In a study by Chou et al. [1985a], comparisons were made of the local SARs in eight brain sites of rats exposed under seven exposure conditions, including exposure in a circular waveguide with the head or tail of an animal facing the radiation source, near field and far field exposures with either E- or H-field parallel to the long-axis of the body, and dorsal exposure in a miniature anechoic chamber with E- or H-field parallel to the long axis of the body. Statistical analysis of the data showed that a) there was a significant difference in local SARs in the eight brain regions measured under each exposure condition, and b) the pattern of energy absorption in different regions of the brain depended on the exposure condition. However, it must be pointed out that in another study [Ward et al., 1986], no temperature 'hot spots' were detected in the brains of rat carcasses and anesthetized rats after irradiation with 2450-MHz RFR. Temperature increases in various regions of the brain were found to be uniform and dependent on the power density of the radiation.

A question that one might ask is whether different absorption patterns in the brain or body could elicit different biological responses in the animal. If this is positive, possible outcomes from the study of bioelectromagnetics research are: (1) a response will be elicited by some exposure conditions and not by others, and (2) different response patterns are elicited by different exposure conditions, even though the average dose rates in the conditions are equal. We [Lai et al., 1984a] reported a difference in responses to the hypothermic effects of pentobarbital depending on whether the rat was exposed with its head facing toward or away from the source of radiation in the waveguide with the average whole body SAR under both conditions remaining the same; however, the patterns of energy absorption in the body and the brain differed in the two exposure conditions. Studies of HACU activity in the different regions of the brain [Lai et al., 1988] also showed that different responses could be triggered using different exposure systems or different waveforms of RFR (continuous-wave or pulsed) with the average whole body SAR held constant under each exposure condition. These data indicate that the energy distribution in the body and other properties of the radiation can be important factors in determining the outcome of the biological effects of RFR. A series of studies by Frei et al. [1989a,b] also demonstrated some interesting results on this issue. The effects of high intensity 2450- and 2800-MHz RFRs on heart rate, blood pressure, and respiratory rate in ketamine-anesthetized rats were studied. Both frequencies produced increases in heart rate and blood pressure and no significant difference was observed whether continuous-wave or pulsed radiation was used. A difference was observed, however, when the animals were exposed with their bodies parallel to the H- or E-field. In the case of 2450-MHz RFR, the E-orientation exposure produced greater increases in heart rate and blood pressure than the H-orientation exposure; whereas no significant difference in the effects between the two exposure orientations was observed with the 2800-MHz radiation. The authors speculated that the differences could be attributed to the higher subcutaneous temperature and faster rise in colonic temperature in the E-orientation when the rats were exposed at 2450 MHz than at 2800 MHz. Once again, this points out that subtle differences in exposure parameters could lead to different responses. Therefore, due to the peculiar pattern of energy deposition and heating by RFR, it may be impossible to replicate the thermal effect of RFR by general heating, i.e., use of temperature controls.

The fact that dosimetry data were based on stationary models that usually show discrete patterns of energy absorption, further complicate the matter. In animal studies, unless the animal is restrained, the energy absorption pattern changes during the exposure period depending on the position and the orientation of the animal. A possible solution would be to perform long-term exposure experiments, thus, the absorption pattern on the average would be made more uniform.

Another important consideration regarding the biological effects of RFR is the duration or number of exposure episodes. This is demonstrated by the results of some of the studies on the neurological effects of RFR. Depending on the responses studied in the experiments, several outcomes could result: an effect was observed only after prolonged (or repeated) exposure, but not after acute exposure [Baranski, 1972; Baranski and Edelwejn, 1968, 1974; Mitchell et al., 1977; Takashima et al., 1979], an effect disappeared after prolonged exposure suggesting habituation [Johnson et al., 1983; Lai et al., 1987c, 1992a], and different effects were observed after different durations of exposure [Baranski, 1972; Dumanski and Shandala, 1974; Grin, 1974; Lai et al., 1989a, 1989b; Servantie et al., 1974; Snyder, 1971]. All of these different responses reported can be explained as being due to the different characteristics of the dependent variable studied. An interesting question related to this is whether or not intensity and duration of exposure interact, e.g., can exposure to a low intensity over a long duration produce the same effect as exposure to a high intensity radiation for a shorter period?

Thus, even though the pattern or duration of RFR exposure is well-defined, the response of the biological system studied will still be unpredictable if we lack sufficient knowledge of the response system. In most experiments on the neurological effects of RFR, the underlying mechanism of the dependent variable was not fully understood. The purpose of most of the studies was to identify and characterize possible effects of RFR rather than the underlying mechanisms responsible for the effects. This lack of knowledge of the response system studied is not uncommon in biological research. In this regard, it may be appropriate to compare the biological and neurological effects of RFR with those of ethanol. Both entities exert non-specific effects on multiple organs in the body. Their effects are nonspecific, because both ethanol and RFR are not acting on specific receptors. The biological effects of ethanol could be a general action on cell membrane fluidity.

In reviewing the literature on the neurological effects of ethanol, one notices some similarity with those of RFR. In both cases, a wide variety of neurological processes were reported to be affected after exposure, but without a known mechanism. On the other hand, inconsistent data were commonly found. For example, in the case of the effects of ethanol on dopamine receptors in the brain, an increase [Hruska, 1988; Lai et al., 1980], a decrease [Lucchi et al., 1988; Syvalahti et al., 1988], and no significant change [Muller, 1980; Tabakoff and Hoffman, 1979] in receptor concentration have been reported by different investigators. Such inconsistencies have existed since the late 70's and there has been no satisfactory explanation for them. Similar research findings of increase, decrease, and no significant change in the concentration of muscarinic cholinergic receptors in the cerebral cortex of animals treated with ethanol have also been reported in the literature [Kuriyama and Ohkuma, 1990]. Dosage and route of ethanol treatment, the frequency of administration, and the species of animal studied, etc., could all attribute to variations in the findings [Keane and Leonard, 1989]. As we have discussed earlier, such considerations on the parameters of treatment also apply to the study of the biological effects of RFR. These are further complicated by the special properties of the radiation, such as waveform and modulation. In addition, RFR effects could have rapid onset and offset when the source was turned on and off, whereas the biological effect of ethanol depends on the rates of absorption and metabolism.

Thus, an understanding of the response characteristics of the dependent variables to different parameters of RFR, such as power density, frequency, waveform, etc., is important. Lack of knowledge about such characteristics may explain some of the discrepancies in bioelectromagnetics research results in the literature. Non-linear response characteristics are frequently observed in biological systems, because different mechanisms are involved in producing a response. For example, in the case of apomorphine-induced locomotor activity, a low dose of apomorphine (e.g., 0.1 mg/kg) decreases locomotor activity, whereas a higher dosage (e.g., 1.0 mg/kg) of the drug causes a profound enhancement. A dose in between may cause an insignificant effect. An explanation for this phenomenon is that a low dose of apomorphine activates selectively presynaptic dopamine receptors in the brain, which decreases dopamine release from its terminals and, thus, a decrease in motor activity. At a high dose, apomorphine stimulates the postsynaptic dopamine receptors, leading to an increase in motor activity.

Another common response-characteristic is the inverted-U function. In this situation, a response is only seen at a certain dose range and not at higher or lower dosages. An example of an inverted-U dose-response function is the effect of benzodiazepines on schedule controlled operant behavior. There is not a good explanation for the occurrence of this function. One possible explanation might be that at least two mechanisms, a facilitatory and an inhibitory function, are involved in the response. At a lower dose range of the drug, for example, the facilitatory mechanism predominates and leads to enhancement of the response, whereas, as the dosage increases an inhibitory mechanism is activated, leading to a decline in response. Thus, it is essential that the dose-response function be determined.

The inverted-U response-characteristic can be the basis of some of the 'window' effects reported in bioelectromagnetics research. Thus, with the above considerations, it is not surprising that RFR can cause enhancement, decrement, and no significant effect on a particular response depending upon the exposure conditions. Blackman et al. [1991] stated on the effect of temperature on calcium ion efflux from brain tissue that, "... either outcome (*inhibition or enhancement in release of calcium ions*), or a null result, is possible, depending on the temperature of tissue sample before and during exposure". However, it must be pointed out that the inverted-U function is not sufficient to account for the 'multiple window' effect reported in one of Blackman's studies [Blackman et al., 1989].

Another important consideration in the study of the central nervous system should be mentioned here. It is well known that the functions of the central nervous system can be affected by activity in the peripheral nervous system. Thirty years ago, McAfee [1961, 1963] pointed out that the thermal effect of RFR on the peripheral nervous system can lead to changes in central nervous system functions and behavior in the exposed animal. This is especially important in the in vivo experiments when the whole body is exposed. However, in most experiments studying the effects of RFR on the central nervous system, the possibility of contribution from the peripheral nervous system was not excluded in the experimental design. Therefore, caution should be taken in concluding that a neurological effect resulted solely from the action of RFR on the central nervous system.

An interesting question arose, whether or not RFR could produce 'non-thermal' biological effects. Many have speculated whether RFR can directly affect the activity of excitable tissues. Schwan [1971, 1977] pointed out that it would take a very high intensity of RFR to directly affect the electrical activity of a cell. On the other hand, Wachtel et al. [1975] have speculated that an RFR-induced polarized current in the membrane of a neuron could lead to changes in activity. Adey [1988] has suggested that cooperative processes in the cell membrane might be reactive to the low energy of oscillating electromagnetic field, leading to a change in membrane potential. Pickard and Barsoum [1988] recorded from cells of the Characeae plant exposed to 0.1-5 MHz pulsed RFR and observed a slow and fast component of change in membrane potential. The slow component was temperature dependent and the fast component was suggested to be produced by rectification of the oscillating electric field induced by RFR on the cell membrane. However, the effect disappeared when the frequency of radiation reached ~10 MHz.

An extreme example of the direct interaction of electromagnetic radiation with a specific biological molecule triggering a neurological effect is the rhodopsin molecules in the rod photorecepter cells that transduce light energy into neural signals. In 1943, a psychophysical experiment by Hecht et al. [1942] suggested that a single photon could activate a rod cell. The molecular biology of rhodopsin is now well understood. It is now known that a single photon can activate a single molecule of rhodopsin. A photon of the visible spectrum turns 11-cis retinol, a moiety of the rhodopsin molecule, to an all-trans form. This triggers a cascade of molecular activities involving specific G-protein, the conversion of cyclic-GMP to 5'-GMP, and eventually closing the sodium-ion channels on the cell membrane of the rod cell. This cascade action leads to a powerful amplification of the photon signal. It was estimated that one photon can affect several hundred C-GMP molecules. Such change is enough to hyperpolarize a rod cell and lead to signal transmission through its synapse [Liebman et al., 1987; Stryer, 1987]. Can a similar molecular sensitive to RFR exist? The problem is that RFR energy is several orders of magnitude (~10^6) lower than that of a photon at the visual spectrum. It is difficult to visualize a similar molecular mechanism sensitive enough to detect RFR.

Another consideration is that the ambient level of RFR is very low in the natural environment and could not have generated enough selection pressure for the evolutionary development of such a molecular mechanism. On the other hand, there may be some reason for the development of a molecular mechanism for the detection of static or low frequency electric or magnetic fields. An example is the electroreception mechanism of two Australian monotremes, the platypus, *Ornithorhynchus anatinus*, and the echidna, *Tachyglossus aculeatus* [Gregory et al., 1989a,b; Iggo et al., 1992; Scheich et al., 1986]. Apparently, receptors sensitive to low-level electric fields exist in the snout and bill of these animals, respectively. Electrophysiological recordings from the platypus show that receptors in the bill can be sensitive to a static or sinusoidally changing (12-300 Hz) electric field of 4-20 mV/cm, and cells in the cerebral cortex can respond to a threshold field of 300 μV/cm. Moreover, behavioral experiments showed that the platypus can detect electric fields as small as 50 μV/cm. In the echidna snout, receptors can respond to fields of 1.8-73 mV/cm. These neural mechanisms enable the animals to detect muscular movements of their prey, termites and shrimps. It would be interesting to understand the transduction mechanism in the electroreceptors in these animals. However, it remains to be seen whether RFR can generate a static or ELF field in tissue and that a similar electroreceptor mechanism exists in other mammals.

Another possible explanation suggested for the neurological effects of RFR is stress. This hypothesis has been proposed by Justesen et al. [1973] and Lu et al. [1980] and based on high intensity of exposure. We have also proposed recently that low-level RFR may be a 'stressor' [Lai et al., 1987a]. Our speculation is based on the similarity of the neurological effects of known stressors (e.g., body-restraint, extreme ambient temperature) and those of RFR (see Table 1 in Lai et al., 1987a). Our recent experiments suggesting that low-level RFR activates both endogenous opioids and corticotropin-releasing factor in the brain further support this hypothesis. Both neurochemicals are known to play important roles in an animal's responses to stressors [Amir et al., 1980; Fisher, 1989]. However, it is difficult to prove that an entity is a stressor, since the criteria of stress are not well defined and the caveat of stress is so generalized that it has little predictive power on an animal's response.

In conclusion, I believe the questions on the biological effects of RFR and the discrepancies in research results in the literature can be resolved by (a) a careful and thorough examination of the effects of the different radiation parameters, and (b) a better understanding of the underlying mechanisms involved in the responses studied. With these considerations, it is very unlikely that the neurological effects of RFR can be accounted for by a single unifying neural mechanism.

ACKNOWLEDGMENTS

The author's research was supported by a grant from the National Institute of Environmental Health Sciences (ES-03712). I thank Mrs. Monserrat Carino, Dr. Chung-Kwang Chou, and Dr. Akira Horita for reviewing the manuscript, and especially Mrs. Dorothy Pratt for her patience and endurance in typing and editing the manuscript numerous times.

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Appendix 9-B - Memory and Behavior

Presention: The Biological Effects, Health Consequences and Standards for Pulsed Radiofrequency Field. International Commission on Nonionizing Radiation Protection and the World Health Organization, Ettoll Majorare, Centre for Scientific Culture, Italy, 1999.

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The nervous system is very sensitive to environmental disturbance. In the proceedings of an international symposium on the "Biological Effects and Health Hazard of Microwave Radiation" hold in Warsaw, Poland in 1973, it was stated in a summary section that 'the reaction of the central nervous system to microwaves may serve as an early indicator of disturbances in regulatory functions of many systems' [Czerski et al., 1974].

Disturbance to the nervous system leads to behavioral changes. On the other hand, alteration in behavior would imply a change in function of the nervous system. Studies on the effect of radiofrequency radiation (RFR) on behavior have been carried out since the beginning of Bioelectromagnetics research. Some of these studies are briefly reviewed below.

It has been speculated that a pulsed RFR is more potent than its continuous-wave (CW) counterpart in causing biological effects [e.g., Barenski, 1972; Frey et al., 1975; Oscar and Hawkins, 1977]. To evaluate this, it is necessary to compare the effects of pulsed RFR with those of CW radiation. Thus, studies on both CW and pulsed (and frequency-modulated) RFRs are included in this review. Comparing the effects of CW and pulsed RFR can actually be related to the popular debate on the distinction between 'thermal' and 'non-thermal/athermal' effect. If an effect is elicited by a pulsed RFR but not by a CW RFR of the same frequency and intensity under the same exposure conditions, it may imply the existence of 'non-thermal/athermal' effect.

Behavior is generally divided into two main categories: spontaneous and learned. Effects of RFR exposure on both types of behavior have been investigated.

Spontaneous Behavior

Spontaneous behaviors are generally considered to be more resistant to disturbance. The most well studied spontaneous behavior in Bioelectromagnetics research is motor (locomotor) activity. Change in motor activity is generally regarded as an indication of change in the arousal state of an animal.

Hunt et al. [1975] reported decreased motor activity in rats after 30 min of exposure to pulsed 2450-MHz RFR (2.5 msec pulses, 120 pps, SAR 6.3 $W \cdot kg^{-1}$). Mitchell et al. [1988] also observed a decrease in motor activity in rats after 7 hr of exposure to CW 2450-MHz RFR (10 $mW·cm^{-2}$, average SAR 2.7 $W·kg^{-1}$).

Roberti [1975] reported no significant change in locomotor activity in rats after long-term (185-408 h) exposure to RFR of different frequencies (10.7-GHz CW; 3-GHz CW; 3-GHz with 1.3 ms pulses and 770 pps) and various intensities (SAR 0.15-7.5 $W·kg^{-1}$). Mitchell et al. [1977] reported an increase in motor activity on a small platform of rats exposed to 2450-MHz RFR (CW, average SAR 2.3 $W·kg^{-1}$, 5 hr/day, 5 days/week for 22 weeks). Motor activity of the RFR exposed rats increased during the first week of exposure and stayed higher than controls throughout the period of the experiment. D'Andrea et al. [1979, 1980] reported decreased motor activity on a stabilimetric platform and no significant change in running wheel activity measured overnight in rats exposed to a 2450-MHz RFR (CW, 5 $mW·cm^{-2}$, SAR 1.2 $W·kg^{-1}$, exposed 5 day/week with a total exposure time of 640 hrs, activity was measured every 2-weeks). However, they reported no significant effect in both behaviors in rats similarly exposed to a 915-MHz RFR even at a higher energy absorption rate (CW, 5 $mW·cm^{-2}$, SAR 2.5 $W·kg^{-1}$). Moe et al. [1976] reported a decrease in motor activity of rats exposed to 918 MHz RFR (CW, SAR 3.6-4.2 $W·kg^{-1}$) during the dark period of the light-dark cycle in a chronic exposure experiment (10 hr/night for 3 weeks). Lovely et al. [1977] repeated the experiment using a lower intensity (2.5 $mW·cm^{-2}$, SAR 0.9 $W·kg^{-1}$, 10 hr/night, 13 weeks) and found no significant change in motor activity in the exposed rats. Thus, the threshold of response under their exposure conditions is between1 and 4 $W·kg^{-1}$.

The results from the above studies indicate that it would need a rather high energy absorption rate (>1 $W·kg^{-1}$) to affect motor activity in animals. However, there are two studies reporting effects on motor activity at relatively low SARs. In a long-term exposure study, Johnson et al. [1983] exposed rats to pulsed 2450-MHz RFR (10 ms pulses, 800 pps) from 8 weeks to 25 months of age (22 hr/day). The average whole body SAR varied as the weight of the rats increased and was between 0.4-0.15 $W·kg^{-1}$. Open field activity was measured in 3-min sessions with an electronic open-field apparatus once every 6 weeks during the first 15 months and at 12-week intervals in the final 10 weeks of exposure. They reported a significantly lower open field activity only at the first test session, and a rise in the blood corticosterone level was also observed at that time. The authors speculated that RFR might be ‘minimally stressful’ to the rats. Rudnev et al. [1978] studied the behavior of rats exposed to CW 2375-MHz RFR at 0.5 $mW·cm^{-2}$ (SAR 0.1 $W·kg^{-1}$), 7 h/day for 1 month. They reported a decrease in balancing time in a treadmill and inclined rod and motor activity in an open-field after 20 days of exposure. The open-field motor activity was found to be increased at 3 months post-exposure. Interestingly, Frey [1977] also reported a decrease in motor coordination on a motor-rod in rats exposed to a 1300-MHz pulsed RFR (0.5 ms pulses, 1000 pps, average power density of 0.65 or 0.2 $mW·cm^{-2}$).

Another type of spontaneous behavior studied was consummatory behavior. In the Rudnev et al. [1978] study, the authors reported a decrease in food intake in their animals after long-term exposure to CW RFR at 0.1 $W·kg^{-1}$. Ray and Behari [1990] also reported a decrease in eating and drinking behavior in rats exposed for 60 days (3 hr/day) to a 7.5-GHz RFR (10-KHz square wave modulation) at an SAR of 0.0317 $W·kg^{-1}$ (average power density 0.6 $mW·cm^{-2}$).

Learned behavior

Several psychological studies have been carried out to investigate whether animals can detect RFR. One of the early studies was that of King et al. [1971] in which RFR was used as the cue in a conditioned suppression experiment. In conditioned suppression, an animal is first trained to elicit a certain response (e.g., bar-press for food). Once a steady rate of response is attained, a stimulus (e.g., a tone) will be presented to signify the on coming of a negative reinforcement (e.g., electric foot shock). The animal will soon learn the significance of the stimulus and a decrease in responding (conditioned suppression) will occur immediately after the presentation of the stimulus. In the experiment of King et al. [1971], rats were trained to respond at a fixed-ratio schedule for sugar water reward. In a 2-hr session, either a tone or RFR would be presented and occasionally followed by an electric foot shock. Radiofrequency radiation of 2450 MHz, modulated at 12 and 60 Hz and at SARs of 0.6, 1.2, 2.4, 4.8, and 6.4 $W \cdot kg^{-1}$ was used as the conditioned stimulus. With training, consistent conditioned suppression was observed with the radiation at 2.4 $W \cdot kg^{-1}$ and higher. This indicates that rats can detect RFR at 2.4 $W \cdot kg^{-1}$. Monahan and Henton [1977] also demonstrated that mice could be trained to elicit a response in order to escape or avoid RFR (CW, 2450-MHz, 40 $W \cdot kg^{-1}$). In another experiment, Carroll et al. [1980] showed that rats did not learn to go to a 'safe' area in the exposure cage in order to escape exposure to RFR (918-MHz, pulse modulated at 60 Hz, SAR 60 $W \cdot kg^{-1}$) (i.e., entering the 'safe' area resulted in an immediate reduction of the intensity of the radiation), whereas the animals learned readily to escape from electric foot shock by going to the 'safe' area. In a further study from the same laboratory, Levinson et al. [1982] showed that rats could learn to enter a 'safe' area, when the RFR was paired with a light stimulus. Entering the area would turn off both the radiation and light. They also showed that rats could learn to escape by entering the 'safe' area when RFR was presented alone, but learned at a lower rate than when the RFR was paired with a light. All these studies indicate that animals can detect RFR, probably as a thermal stimulus.

One of the most well established effects of pulsed RFR is the 'auditory effect'. Neurophysiological and psychological experiments indicate that animals can probably perceive microwave pulses as a sound stimulus [Chou et al., 1982a; Lin, 1978]. In a series of experiments, Frey and his associates [Frey and Feld, 1975; Frey et al., 1975] demonstrated that rats spent less time in the unshielded compartment of a shuttlebox, when the box was exposed to 1200-MHz pulsed RFR (0.5-ms pulses, 1000 pps, average power density 0.2 $mW \cdot cm^{-2}$, peak power density 2.1 $mW \cdot cm^{-2}$) than during sham exposure. When a CW RFR (1200-MHz, 2.4 $mW \cdot cm^{-2}$) was used, rats showed no significant preference to remain in the shielded or unshielded side of the box. Hjeresen et al. [1979] replicated this finding using pulsed 2880-MHz RFR (2.3 ms pulses, 100 pps, average power density 9.5 $mW \cdot cm^{-2}$) and showed that the preference to remain in the shielded side of a shuttlebox during RFR exposure could be generalized to a 37.5-kHz tone. Masking the 'radiation-induced auditory effect' with a 10-20 kHz noise also prevented shuttlebox-side preference during pulsed RFR exposure. These data indicate that the pulsed RFR-induced 'avoidance' behavior is due to the auditory effect.

The question is why rats avoid pulsed RFR? Is the 'auditory effect' stressful? This question was recently raised by Sienkiewicz [1999]. In an attempt to replicate our radial-arm experiment (Lai et al., 1989), he exposed mice to 900-MHz radiation pulsed at 217 Hz for 45 min a day for 10 days at a whole body SAR of 0.05 $W \cdot kg^{-1}$. He didn't observe any significant effect of RFR exposure on maze learning, but reported that 'some of the exposed animals in our experiment appeared to show a stress-like response during testing in the maze. The animals tested immediately after exposure showed a more erratic performance, and were slower to complete the task compared to the animals tested after a short delay following exposure. This pattern of behavior may be consistent with increased levels of stress.' He also reported that exposed animals showed increased urination and defecation. He speculated that these behavioral effects were caused by the ‘auditory effect’ of the pulsed RFR.

Many studies investigated the effects of RFR exposure on schedule-controlled behavior. A schedule is the scheme by which an animal is rewarded (reinforced) for carrying out a certain behavior. For example, an animal can be reinforced for every response it makes, or reinforced intermittently upon responding according to a certain schedule (e.g., once every ten responses). Schedules of different complexity are used in psychological research. The advantage of using reinforcement schedules is that they generate in animals an orderly and reproducible behavioral pattern that can be maintained over a long period of time. This allows a systematic study of the effect of RFR. Generally speaking, more complex behaviors are more susceptible to disruption by environmental factors. However, the underlying neural mechanisms by which different schedules affect behavior are poorly understood.

In a study by D'Andrea et al. [1977], RFRs of different frequencies and intensities were studied on their effects on bar-pressing rate on a variable-interval schedule. It was found that the latency time of stoppage to respond after the radiation was turned on correlated with the rate of rise in body temperature of the animal. Lebovitz [1980] also studied the effects of pulsed 1300-MHz RFR (1 ms pulses, 600 pps) on rats bar-pressing on a fixed-ratio schedule for food reinforcement. A 15-minute ‘rewarded’ period, when bar pressing was rewarded with food, was followed by a 10-min ‘unrewarded’ period. Both food reinforced bar presses and unrewarded bar presses during the periods were studied. No significant effect was detected in both types of response at SAR of 1.5 $W{\cdot}kg^{-1}$. However, at 6 $W{\cdot}kg^{-1}$, there was a slight reduction in rewarded bar presses and a large reduction in unrewarded bar presses. The authors concluded that the unrewarded behavior was more susceptible to the effect of RFR than the rewarded behavior. However, Hunt et al. [1975] trained rats to bar press for saccharin water rewards in the presence (5- second duration) of a flashing light and not to respond in the presence of a tone. After 30 min of exposure to 2450-MHz RFR (modulated at 20 Hz, SAR of 6.5 or 11.0 $W{\cdot}kg^{-1}$), rats made more misses at the presence of the light, but there were no significant changes in the incidences of bar-pressing error when the tone was on (unrewarded). Gage [1979] trained rats to alternate responses between 2 levers at 11-30 times for a food reinforcement. Decrement in response rates was observed after 15 hrs of exposure to CW 2450-MHz RFR at 10, 15, and 20 $mW{\cdot}cm^{-2}$ (0.3 $W{\cdot}kg^{-1}$ per $mW{\cdot}cm^{-2}$).

Effects of RFR on more complex operant response sequence and reinforcement schedules were studied in various experiments. de Lorge and Ezell [1980] tested rats on an auditory vigilance (observing-response) behavioral task during exposure to pulsed 5620-MHz (0.5 or 2 ms, 662 pps) and 1280-MHz (3 ms, 370 pps) RFR. In this task, rats had to discriminate two tones in order to press one of two bars appropriately for food reinforcement. The task required continuous sensory-motor activities in which the animal had to coordinate its motor responses according to the stimulus cues (tone) presented. Behavioral decrement was observed at a SAR of 3.75 $W{\cdot}kg^{-1}$ with the 1280-MHz radiation, and at 4.9 $W{\cdot}kg^{-1}$ with the 5620-MHz radiation. The authors concluded that ‘…the rat’s observing behavior is disrupted at a lower power density at 1.28 than at 5.62 GHz because of deeper penetration of energy at the lower frequency, and because of frequency-dependent differences in anatomic distribution of the absorbed microwave energy.’ In another experiment, de Lorge [1984] studied rhesus monkeys trained on the auditory vigilance (observing-response) task. After the training, the effects of exposure to RFR of different frequencies (225, 1300, and 5800 MHz) were studied [225-MHz-CW; 1300-MHz- 3 ms pulses, 370 pps; 5800-MHz- 0.5 or 2 ms pulses, 662 pps]. Reduction in performance was observed at different power density thresholds for the frequencies studied: 8.1 mW·cm^{-2} (SAR 3.2 W·kg^{-1}) for 225 MHz, 57 mW·cm^{-2} (SAR 7.4 W·kg^{-1}) for 1300 MHz, and 140 mW·cm^{-2} (SAR 4.3 W·kg^{-1}) for 5800 MHz. de Lorge concluded that the behavioral disruption under different frequencies of exposure was more correlated with change in body temperature. Disruption occurred when the colonic temperature of the animal had increased by 1^{o}C.

Thomas et al. [1975] trained rats to bar press on two bars: a fixed ratio of 20 on the right bar (20 bar presses produced a food pellet reward) and differential reinforcement of low rate (DRL) on the left bar (bar presses had to be separated by at least 18 sec and no more than 24 sec to produce a reward). There was a time-out period between schedules, i.e., no reinforcement available for responding. Animals were tested 5-10 min after 30 min of exposure to either CW 2450-MHz, pulsed 2860-MHz (1 ms pulses, 500 pps) or pulsed 9600-MHz (1 ms pulses, 500 pps) RFR at various power densities. An increase in DRL response rate was observed with 2450-MHz radiation >7.5 mW·cm^{-2} (SAR 2.0 W·kg^{-1}), 2860-MHz RFR >10 mW·cm^{-2} (2.7 W·kg^{-1}), and 9600-MHz RFR >5 mW·cm^{-2} (SAR 1.5 W·kg^{-1}). A decrease in the rate of response at the fixed ratio schedule was seen in all three frequencies when the power density was greater than 5 mW·cm^{-2}. In addition, an increase in response rate was observed during time-out periods under irradiation of the three frequencies of RFR at greater than 5 mW·cm^{-2}. This indicates a disruption of the animals' ability to discriminate the different schedule situations.

Schrot et al. [1980] trained rats to learn a new daily sequence of pressing of three bars for food reinforcement. An increased number of errors and decreased learning rates were observed in the animals after 30 min of exposure to pulsed 2800-MHz RFR (2 ms pulses, 500 pps) at average power densities of 5 and 10 mW·cm^{-2} (SAR 0.7 and 1.7 W·kg^{-1}, respectively). No significant effect on performance was observed at power densities of 0.25, 0.5, and 1 mW·cm^{-2}.

D'Andrea et al. [1989] studied the behavioral effects of high peak power RFR pulses of 1360-MHz. Rhesus monkeys performing on a complicated reinforcement-schedule involving time-related behavioral tasks (inter-response time, time discrimination, and fixed interval responses) were exposed to high peak power RFR (131.8 W·cm^{-2} rms, pulse repetition rate 2-32 Hz). No significant disturbance in performance was observed in the monkeys. Akyel et al. [1991] also studied the effects of exposure to high peak power RFR pulses on behavior. In their experiment, rats pre-trained to bar-press for food reinforcement on either fixed ratio, variable interval, or DRL schedule were exposed for 10 min to 1250-MHz pulses. Each pulse (10 ms width) generated a whole body specific absorption of 2.1 J·kg^{-1}, which corresponds to a whole body average SAR of 0.21 mW·kg^{-1}. The pulse rate was adjusted to produce different total doses (0.5-14 kJ·kg^{-1}). Only at the highest dose (14 kJ·kg^{-1}), stoppage of responding was observed after exposure, when the colonic temperature was increased by ~2.5^{o}C. Responding resumed when colonic temperature returned to within 1.1^{o}C above the pre-exposure level. When responding resumed, the response rates on the fixed ratio and variable interval schedules were below the pre-exposure base line level. Responses on the DRL schedule were too variable to allow a conclusion to be drawn. The authors concluded that the effect of the high peak power RFR pulses on schedule-controlled behavior was due to hyperthermia.

Several studies investigated the effects of <u>long-term</u> RFR exposure on schedule controlled-behavior. Mitchell et al. [1977] trained rats to respond on a mixed schedule of reinforcement (FR-5 EXT-15 sec), in which 5 responses would give a reward and then a 15 sec lapse time (extinction period) was required before a new response would be rewarded. In addition, the schedule of reinforcement was effective when a lamp was on, while no reinforcement was given when the lamp was off. Rats were then exposed to CW 2450-MHz

RFR (average SAR 2.3 $W \cdot kg^{-1}$) for 22 weeks (5 hr/day, 5 days/week) and tested at different times during the exposure period. The RFR-exposed rats showed higher responses during the extinction period, indicating poorer discrimination of the response cues. Navakatikian and Tomashevskaya [1994] described a complex series of experiments in which they observed disruption of a behavior (active avoidance) by RFR. In the study, rats were first trained to perform the behavior and then exposed to either CW 2450-MHz RFR or pulsed 3000-MHz RFR (400-Hz modulation, pulse duration 2 ms, and simulation of radar rotation of 3, 6, and 29 rotations/min) for 0.5-12 hrs or 15-80 days (7-12 hr/day). Behavioral disruption was observed at a power density as low as 0.1 $mW \cdot cm^{-2}$ (0.027 $W \cdot kg^{-1}$).

Two series of well-designed experiments were run by D'Andrea and his colleagues to investigate the effects of chronic RFR exposure on behavior. In one experiment [D'Andrea et al., 1986 a], rats were exposed for 14 weeks (7 hr/day, 7 days/week) to CW 2450-MHz RFR at 2.5 $mW \cdot cm^{-2}$ (SAR 0.7 $W \cdot kg^{-1}$). After exposure, the rats were trained to bar press on an interresponse time criterion (IRT). In this schedule, the animals had to respond within 12 to 18 sec after the previous response in order to receive a food reward. Radiofrequency radiation exposed rats emitted more responses during the training period. When the training was completed, the RFR-exposed rats had lower efficiency in bar-pressing to obtain food pellets, i.e., they made more inappropriate responses and received fewer food pellets than the sham-exposed rats during a session. In a signalled two-way active avoidance shuttlebox test, the RFR-exposed rats showed less avoidance response than the sham-exposed rats during training; however, no significant difference in responses in the shuttlebox test was detected at 60 days after exposure between the RFR- and sham-exposed animals. In this experiment, a decrease in the threshold of electric foot shock detection (i.e., increase in sensitivity) was also observed in the irradiated rats during the exposure period, and an increased open-field exploratory behavior was observed in the rats at 30 days post-exposure. It may be interesting to point out that Frey [1977] also reported a decrease in tail pinch-induced aggressive behavior in RFR-exposed rats. Increased latency, decrease in duration, and episodes of fighting after tail pinching were observed between two rats being irradiated with RFR. This could be due to a decreased sensitivity or perception of pain and the RFR-induced activation of endogenous opioids described below.

In a second experiment [D'Andrea et al., 1986 b], rats were exposed to 2450-MHz RFR at 0.5 $mW \cdot cm^{-2}$ (SAR 0.14 $W \cdot kg^{-1}$) for 90 days (7 hr/day, 7 days/week). Open-field behavior, shuttlebox performance, and schedule-controlled bar-pressing behavior for food pellets were studied at the end of the exposure period. A small deficit in shuttlebox performance and an increased rate of bar-pressing were observed in the RFR exposed rats. Summarizing the data from these two series of experiments [D'Andrea et al., 1986 a,b], D'Andrea and his co-workers concluded that the threshold for the behavioral and physiological effects of chronic RFR exposure in the rats studied in their experiments occurred between the power densities of 0.5 $mW \cdot cm^{-2}$ (SAR 0.14 $W \cdot kg^{-1}$) and 2.5 $mW \cdot cm^{-2}$ (SAR 0.7 $W \cdot kg^{-1}$).

In a further experiment, DeWitt et al. [1987] also reported an effect on an operant task in rats after exposure for 7hr/day for 90 days to CW 2450-MHz RFR at a power density of 0.5 $mW \cdot cm^{-2}$ (0.14 $W \cdot kg^{-1}$).

Little work has been done to investigate the effects of RFR on memory functions. We [Lai et al., 1989] studied the effect of short-term (45 min) RFR exposure (2450-MHz, 2 msec pulses, 500 pps, 1 $mW \cdot cm^{-2}$, SAR 0.6 $W \cdot kg^{-1}$) on the rats' performance in a radial-arm maze, which measures spatial working (short-term) memory function. The maze consists of a central circular hub with arms radiating out like the spokes of a wheel. In this task, food-deprived animals are trained to explore the arms of the maze to obtain food reinforcement at the end of each arm. In each session they have to enter each arm once and a reentry is considered as an error. This task requires 'working memory', i.e., the rat has to remember the arms it has already entered during the course of a session. We found that short-term (45 min) exposure to RFR before each session of maze running significantly retarded the rats' abilities to perform in the maze. They made significantly more errors than the sham-exposed rats. In a further experiment [Lai et al., 1994], we found that the RFR-induced working memory deficit in the radial-arm maze was reversed by pretreating the rats before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter systems inside the central nervous system are involved in the RFR-induced spatial working memory deficit. Spatial working memory requires the functions of the cholinergic innervations in the frontal cortex and hippocampus. The behavior result agrees with our previous neurochemical findings that RFR exposure decreased the activity of the cholinergic systems in the frontal cortex and hippocampus of the rats [Lai et al., 1987]. Endogenous opioids [Lai et al., 1992] and the ‘stress hormone’ corticotropin-releasing factor [Lai et al., 1990] are also involved. Our hypothesis is that radiofrequency radiation activates endogenous opioids in the brain, which in turn cause a decrease in cholinergic activity leading to short-term memory deficit. Related to this that there is a report by Kunjilwar and Behari [1993] showing that long-term exposure (30-35 days, 3 hrs/day, SAR 0.1-0.14 W/kg) to 147-MHz RFR and its sub-harmonics 73.5 and 36.75 MHz, amplitude modulated at 16 and 76 Hz, decreased acetylcholine esterase activity in the rat brain, whereas short-term exposure (60 min) had no significant effect on the enzyme. There is another report by Krylova et al. [1992] indicating that ‘cholinergic system plays an important role in the effects of electromagnetic field on memory processes’. There are also two studies suggesting the involvement of endogenous opioids in the effects of RFR on memory functions [Krylov et al., 1993; Mickley and Cobb, 1998].

In a more recent experiment, we [Wang and Lai, 2000] studied spatial long-term memory using the water maze. In this test, rats are trained to learn the location of a submerged platform in a circular water pool. We found that rats exposed to pulsed 2450-MHz RFR (2 ms pulses, 500 pps, 1.2 $W \cdot kg^{-1}$, 1 hr) were significantly slower in learning and used a different strategy in locating the position of the platform.

Comments

(1) From the data available, it is not apparent that pulsed RFR is more potent than CW RFR in affecting behavior in animals. Even though different frequencies and exposure conditions were used in different studies and hardly any dose-response study was carried out, there is no consistent pattern that the SARs of pulsed RFR reported to cause an effect are lower than those of CW RFR. For example, the Thomas et al [1975] study showed that the thresholds of effect of CW 2450-MHz (2.0 $W \cdot kg^{-1}$) and pulsed 2860-MHz (2.7 $W \cdot kg^{-1}$) radiation on DRL bar-pressing response are quite similar.

(2) Thermal effect is definitely a factor in the effects reported in some of the experiments described above. A related point is that most psychoactive drugs also affect body temperature. Stimulants cause hyperthermia, barbiturates cause hypothermia, and narcotics have a biphasic effect on body temperature (hyperthermia at low doses and hypothermia at high doses). It is not uncommon to

observe a change of 2-3^{o}C within 30 min after a drug is administered. However, in reviewing the literature, there is no general correlation between the effects of psychoactive drugs on body temperature and schedule-controlled behavior. Thus, body temperature may not be a major factor in an animal's responding under schedule-controlled behavior, at least in the case of psychoactive drugs. On the contrary, some of the experiments described above strongly suggest the role of hyperthermia on the RFR effect on the behavior. Perhaps, a sudden and large increase in body temperature as in the case of RFR can have a major effect on responding.

(3) Generally speaking, when effects were observed, RFR disrupted schedule-controlled behavior in animals such as in the cases of discrimination responding [de Lorge and Ezell, 1980; Hunt et al., 1975; Mitchell et al., 1977], learning [Schrot et al., 1980], and avoidance [D'Andrea et al., 1986 a,b]. This is especially true when the task involved complex schedules and response sequence. In no case has an improvement in behavior been reported in animals after RFR exposure. It is puzzling that only disruptions in behavior by RFR exposure are reported. In the studies on EEG, both excitation (desynchronization) and depression (synchronization) have been reported after exposure to RFR [Bawin et al., 1973; Chizhenkova, 1988; Chou et al., 1982b; Dumansky and Shandala, 1974; Goldstein and Sisko, 1974; Takeshima et al., 1979]. Motor activity has also been reported to increase [D'Andrea et al., 1979, 1980; Frey et al., 1975; Hjeresen et al., 1979; Mitchell et al., 1977; Rudnev et al., 1978] and decrease [Hunt et al., 1975; Johnson et al., 1983; Mitchell et al., 1988; Moe et al., 1976; Rudnev et al., 1978] after RFR exposure. If these measurements can be considered as indications of electrophysiological and behavioral arousal and depression, improvement in behavior should occur under certain conditions of RFR exposure. This is especially true with avoidance behavior. Psychomotor stimulants that cause EEG desynchronization and motor activation improve avoidance behavior, whereas tranquilizers that have opposite effects on EEG and motor activity decrease avoidance behavior.

(4) It is difficult to conclude from the effects of RFR on schedule-controlled behavior the underlying neural mechanisms involved. In general, the effects of the effect of RFR on schedule-controlled behavior is similar to those of other agents, e.g., psychoactive drugs. For example, the way that a certain drug affects schedule-controlled behavior depends on the base line level of responding. A general rule is that drugs tend to decrease the rate when the base line responding rate is high and vice versa. This is known as rate-dependency. Exposure to RFR caused a decrease in response rate when a variable interval schedule that produces a steady rate of responding was used [D'Andrea et al., 1976; 1977], and an increase in responding when the DRL-schedule of reinforcement, that produces a low base line of responding, was used [Thomas et al., 1975]. This may reflect a rate-dependency effect. The effect of an agent can also depend on the schedule of reinforcement. For example, amphetamine has different effects on responses maintained on DRL schedule and punishment-suppressed responding schedule, even though both schedules generate a similar low response rate. Stimulus control as a determinant of response outcome was seen in the study of Lebovitz [1980] when unrewarded responses were disrupted more by RFR than rewarded responses, and the study of Hunt et al. [1975] that showed the reverse relationship. In the former experiment a fixed interval schedule was used, whereas in the latter a discrimination paradigm was studied.

(5) It is also interesting to point out that in most of the behavioral experiments, effects were observed after the termination of RFR exposure. In some experiments (e.g., Rudnev et al., 1978; D’Andrea et al., 1986 a,b), tests were made days after exposure. This suggests a persistent change in the nervous system after exposure to RFR.

(6) In many instances, effects on learned behavior were observed at a SAR less than 4 $W^{\cdot}kg^{-1}$. (D'Andrea et al [1986a,b] 0.14 to 0.7 $W^{\cdot}kg^{-1}$; DeWitt et al. [1987] 0.14 $W^{\cdot}kg^{-1}$; Gage [1979] 3 $W^{\cdot}kg^{-1}$; King et al.[1971] 2.4 $W^{\cdot}kg^{-1}$; Lai et al. [1989] 0.6 $W^{\cdot}kg^{-1}$; Mitchell et al. [1977] 2.3 $W^{\cdot}kg^{-1}$; Navakatikian and Tomashevskaya [1994] 0.027 $W^{\cdot}kg^{-1}$; Schrot et al. [1980] 0.7 $W^{\cdot}kg^{-1}$; Thomas et al. [1975] 1.5 to 2.7 $W^{\cdot}kg^{-1}$; Wang and Lai [2000] 1.2 $W^{\cdot}kg^{-1}$).

(7) Does disturbance in behavior have any relevance to health? The consequence of a behavioral deficit is situation dependent and may not be direct. It probably does not matter if a person is playing chess and RFR in his environment causes him to make a couple of bad moves. However, the consequence would be much more serious if a person is flying an airplane and his response sequences are disrupted by RFR radiation.

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SECTION 10 – Part 1

EVIDENCE FOR BRAIN TUMORS AND ACOUSTIC NEUROMAS

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Prepared for the BioInitiative Working Group
July 2007

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I. Introduction

During the recent decade potential health risks from microwave exposure during use of wireless phones has been discussed both in scientific settings but also by the layman. Especially the use of mobile phones has been of concern, to less extent use of cordless desktop phones (digital enhanced cordless telephone; DECT). The Nordic countries were among the first in the world to widely adopt use of such devices, probably due to the mobile phone companies like Ericsson in Sweden and Nokia in Finland.

These countries may be taken as models for the introduction of this new technology on the market. Thus, the analogue mobile phone system (Nordic Mobile Telephony, NMT) using 450 MHz started to operate in Sweden in 1981. First, it was used in cars with external antenna but from 1984 mobile (portable!) phones existed. This system is still used in Sweden but only to a minor extent. The 900 MHz NMT system operated in Sweden between 1986-2000. The GSM phone (Global System for Mobile communication) started in 1991 and is the most used phone type today, although the 3G phone (third generation mobile phone, UMTS) is increasingly used now.

The risk of brain tumors has been of special concern since the brain is the organ mainly exposed during such phone calls. Most studies on this topic have been of the case-control design and no results exist from prospective cohort studies. However, the results have been hampered by too short tumor-induction period in most studies or with limited number of long-term users, i.e. $\geq$ 10 years latency time. As to carcinogenesis short latency period is of limited value to predict long-term health risks. Usually a latency period of at least 10 years is needed for more firm conclusions. It should noted that for several carcinogens longer latency periods are often required, such as smoking and lung cancer, asbestos and lung cancer, dioxins and certain cancer types etc.

By now a number of studies exist that give results for brain tumour risk and use of mobile phones for subjects with latency period $\geq$ 10 years. Most of these results are based on low numbers but nevertheless may together give a pattern of increased risk. In this review we discuss all studies on this topic that have been published so far. Moreover, we present a meta-analysis of results from studies with at least 10 years latency period. Only the Hardell group in Sweden has published results also for use of cordless phones. Recently the same group published an overview of long-term use of cellular phones and the risk for brain tumors, especially with use for 10 years or more (Hardell et al 2007). In the following a brief summary is given of these results with the addition of two more study published after that review (Klaeboe et al 2007, Schlehofer et al 2007). For further details see Hardell et al (2007).

II. Materials and Methods

The Pub Med database (**www.ncbi.nlm.nih.gov**) was used for an up-dated search of published studies in this area using mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. Personal knowledge of published studies was also used in order to get as comprehensive review as possible. Regarding several publication of the same study the most recent one with relevant data was used. We identified 20 studies to be included. Two were cohort studies (one study analysed twice) and 18 were case-control studies. No mortality studies were included. Three studies came from USA, four from Denmark, one from Finland, five from Sweden, two from Germany, one from the UK, one from Japan, one from Norway and two from study groups partly overlapping previously mentioned studies.

III. Results

A. The first Swedish studies

The first study by Hardell et al (1999, 2001) included cases and controls collected during 1994-96 in Sweden. Only living cases were included. Two controls were selected to each case from the Population Registry. The questionnaire was answered by 217 (93 %) cases and 439 (94 %) controls. Overall no association between mobile phone use and brain tumours was found, but when analysing ipsilateral phone use a somewhat increased risk was seen especially for tumours in the temporal, occipital or temporoparietal lobe yielding odds ratio (OR) = 2.4, 95 % confidence interval (CI) = 0.97-6.1 (Hardell et al 2001).

Hardell et al (2006a) made a pooled analysis for benign brain tumours from their two case-control studies. Cases were reported from Cancer Registries and controls were population based. The questionnaire was answered by 1,254 (88 %) cases and 2,162 (89 %) controls. Also use of cordless desktop phones was assessed. Use of cellular phones gave for acoustic neuroma OR = 1.7, 95 % CI 1.2-2.3 increasing to OR = 2.9, 95 % CI = 1.6-5.5 with > 10 year latency period. The corresponding results for cordless phones were OR = 1.5, 95 % CI = 1.04-2.0, and OR = 1.0, 95 % CI 0.3-2.9, respectively. Regarding meningioma cellular phones gave OR = 1.1, 95 % CI = 0.9-1.3, and cordless OR = 1.1, 95 % CI = 0.9-1.4. Using > 10 year latency period ORs increased, for cellular telephones OR = 1.5, 95 % CI = 0.98-2.4, and for cordless phones OR = 1.6, 95 % CI = 0.9-2.8.

The pooled analyses of the two case control studies of malignant brain tumours by Hardell et al (2006b) included 905 (90%) cases and the same control group as for benign tumours was used, 2,162 (89 %) subjects. Overall for low-grade astrocytoma cellular phones gave OR= 1.4, 95 % CI = 0.9-2.3 and cordless phones OR = 1.4, 95 % CI = 0.9-3.4. The corresponding results for high-grade astrocytoma were OR = 1.4, 95 % CI = 1.1-1.8, and OR = 1.5, 95 % CI = 1.1-1.9, respectively. Using > 10 year latency period gave for low-grade astrocytoma and use of cellular phones OR = 1.5, 95 % CI = 0.6-3.8 (ipsilateral OR = 1.2, 95 % CI = 0.5-5.8), and for cordless phones OR = 1.6, 95 % CI = 0.5-4.6 (ipsilateral OR = 3.2, 95 % CI = 0.6-16). For high-grade astrocytoma in the same latency period cellular phones gave OR = 3.1, 95 % CI = 2.0-4.6 (ipsilateral OR = 5.4, 95 % CI = 3.0-9.6), and cordless phones OR = 2.2, 95 % CI = 1.3-3.9 (ipsilateral OR = 4.7, 95 % CI = 1.8-13).

B. Studies from USA

Muscat et al (2000) studied patients with malignant brain tumours from five different hospitals in USA. Controls were hospital patients. Data from 469 (82 %) cases and 422 (90 %) controls were available. Overall no association was found, OR for handheld cellular phones was 0.9, 95 % CI = 0.6-1.2, but the mean duration of use was short, only 2.8 years for cases and 2.7 years for controls. For neuroepithelioma OR = 2.1, 95 % CI = 0.9-4.7, was reported. The study is inconclusive since no data were available on long-term users ($\geq$ 10 years latency period). Some support of an association was obtained since of 41 evaluable tumours, 26 occurred at the side of the head mostly used during calls and 15 on the contralateral side.

Also the study by Inskip et al (2001) from USA had few long-term users of mobile phones, only 11 cases with glioma, 6 with meningioma and 5 with acoustic neuroma with $\geq$ 5 years regular use. No subjects had $\geq$ 10 years use. The study comprised 489 (92 %) hospital cases with malignant brain tumours, 197 with meningioma and 96 with acoustic neuroma, and 799 (86 %) hospital-based controls. Overall no significant associations were found. Regarding different types of glioma OR = 1.8, 95 % CI = 0.7-5.1 was found for anaplastic astrocytoma. Duration of use ≥ 5 years gave for acoustic neuroma OR increased to 1.9, 95 % CI = 0.6-5.9.

In another study by Muscat et al (2002) presented results from a hospital based case-control study on acoustic neuroma on 90 (100 %) patients and 86 (100 %) controls. Cell phone use 1-2 years gave OR = 0.5, 95 % CI = 0.2-1.3 (n=7 cases), increasing to OR = 1.7, 95 % CI = 0.5-5.1 (n=11 cases), in the group with 3-6 years use. Average use among cases was 4.1 years and among controls 2.2 years.

C. Danish cohort study

A population based cohort study in Denmark of mobile phone users during 1982 to 1995 included over 700,000 users (Johansen et al 2001). About 200,000 individuals were excluded since they had company paid mobile phones. Of digital (GSM) subscribers only nine cases had used the phone for ≥ 3 years duration yielding standardised incidence ratio (SIR) of 1.2, 95 % CI = 0.6-2.3. No subjects with 10-year use were reported.

This cohort study was updated with follow-up through 2002 for cancer incidence (Schüz et al 2006). There was no truly unexposed group for comparison since a large part of the population uses wireless phones. Moreover the excluded company subscribers (> 200 000 or 32 %) were apparently included in the reference population. There was also a very skewed sex distribution with 85 % men and only 15 % women in the cohort. SIR was significantly decreased to 0.95, 95 % CI = 0.9-0.97 for all cancers indicating a "healthy worker" effect in the study. In the group with ≥ 10 years since first subscription significantly decreased SIR of 0.7, 95 % CI = 0.4-0.95 was found for brain and nervous system tumours indicating methodological problems in the study. No latency data were given or laterality of phone use in relation to tumour localisation in the brain. This study was uninformative regarding long-term health effects from mobile phone use.

D. Finnish study

Auvinen et al (2002) did a register based case-control study on brain and salivary gland tumors in Finland. All cases aged 20-69 years diagnosed in 1996 were included; 398 brain tumour cases and 34 salivary gland tumour cases. The duration of use was short, for analogue users 2-3 years and for digital less than one year. No association was found for salivary gland tumours. For glioma OR = 2.1, 95 % CI = 1.3-3.4 was calculated for use of analogue phones, but no association was found for digital mobile phones. When duration of use of analogue phones was used as a continuous variable an increased risk was found for glioma with OR = 1.2, 95 % CI = 1.1-1.5 per year of use.

E. The Interphone studies

1. Acoustic neuroma

The Swedish part of the Interphone study on acoustic neuroma included exposure data from 148 (93 %) cases and 604 (72 %) population based controls (Lönn et al 2004). Use of digital phones with time $\geq$ 5 years since first use gave OR = 1.2, 95 % CI = 0.7-2.1. No subjects were reported with use of a digital phone $\geq$ 10 years. An association was found for use of analogue phones yielding for $\geq$ 10 years latency period OR = 1.8, 95 % CI = 0.8-4.3 increasing to OR = 3.9, 95 % CI = 1.6-9.5 for ipsilateral use.

In Denmark the Interphone study included 106 (82 %) interviewed cases with acoustic neuroma and 212 (64 %) population-based controls (Christensen et al 2004). Significantly larger tumours were found among cellular phone users, 1.66 cm^3 compared with 1.39 cm^3 among non-users, p =

0.03. However OR was not significantly increased but only two cases had use a mobile phone regularly ≥ 10 years.

Schoemaker et al (2005) presented results for acoustic neuroma as part of the Interphone study performed in 6 different regions in the Nordic countries and UK, as previously partly reported (Lönn et al 2004; Christensen et al 2004). The results were based on 678 (82 %) cases and 3,553 (42 %) controls. Lifetime use of mobile phone for ≥ 10 years gave for ipsilateral acoustic neuroma OR = 1.8, 95 % CI = 1.1-3.1, and for contralateral OR = 0.9, 95 % CI = 0.5-1.8.

The study from Japan by Takebayashi et al (2006) included 101 (84 %) acoustic neuroma cases aged 30-69 years and diagnosed during 2000-2004. Using random digit dialling 339 (52 %) controls were interview. No association was found, OR = 0.7, 95% CI = 0.4 – 1.2. No exposure related increase in the risk of acoustic neuroma was observed when the cumulative length of use (<4 years, 4-8 years, >8 years) or cumulative call time (<300 hours, 300-900 hours, >900 hours) was used as an exposure index. The OR was 1.1, 95% CI = 0.6 - 2.1, when the reference date was set to five years before the diagnosis. Further, laterality of mobile phone use was not associated with tumours. No cases with ≥ 10 years latency period were reported.

Use of mobile phones and risk of acoustic neuroma were published from Norway as part of the Interphone study (Klaeboe et al 2007). It included 45 (68 %) acoustic neuroma cases and 358 (69 %) controls. A decreased risk was found with OR = 0.5, 95 % CI = 0.2-1.0. Using different criteria such as duration of regular use, time since first regular use, cumulative use etc 22 additional ORs and CIs were calculated. Time since first regular use for < 6 years gave OR =

1.0, 95 % CI = 0.2-5.7. All 21 other ORs were < 1.0 indicating systematic bias in the study. No case had a latency period of 10 years.

Schlehofer et al (2007) reported results from the German part of the Interphone study on sporadic acoustic neuroma. The study was performed during October 2000 and October 2003. Four study areas were included and cases were aged 30-59 years, but from October 1, 2001 extended to include the age group 60-69 years. They were recruited from hospitals and included 97 (89 %) cases, however, three with trigeminus neuroma. Controls were randomly selected from population registries and in total 202 (55 %) agreed to participate. No association was found for regular mobile phone use, OR = 0.7, 95 % CI = 0.4-1.2. Most ORs were < 1.0 and a decreasing trend of the risk was found for time since first regular use, lifetime number of use and duration of calls. No case had a latency period > 10 years. However, increased OR was found for highly exposed in "specified occupational exposure" yielding OR = 1.5, 95 % CI =0.5-4.2.

E. The Interphone studies

2. Glioma, meningioma

Lönn et al (2005) also studied glioma and meningioma. Data were obtained for 371 (74 %) glioma and 273 (85 %) meningioma cases. The control group consisted of 674 (71 %) subjects. No association was found although time since first regular phone use for ≥ 10 years gave for ipsilateral glioma OR = 1.6, 95 % CI = 0.8-3.4 and for contralateral glioma OR = 0.7, 95 % CI = 0.3-1.5.

For ipsilateral meningioma OR = 1.3, 95 % CI = 0.5-3.9 was calculated and for contralateral OR = 0.5, 95 % CI = 0.1-1.7 using 10 ≥ years latency period.

The Danish part of the Interphone study on brain tumours (Christensen et al, 2005) included 252 (71 %) persons with glioma, 175 (74 %) with meningioma and 822 (64 %) controls. For meningioma OR = 0.8, 95 % CI = 0.5-1.3 was calculated and for low-grade glioma OR = 1.1, 95 % CI = 0.6-2.0, and for high-grade glioma OR = 0.6, 95 % CI = 0.4-0.9 were found. Use for ≥ 10 years yielded for meningioma OR = 1.0, 95 % CI = 0.3-3.2, low-grade glioma OR = 1.6, 95 % CI = 0.4-6.1 and for high-grade glioma OR = 0.5, 95 % CI = 0.2-1.3. Regarding high-grade glioma 17 ORs were presented and all showed OR < 1.0.

Results from England were based on 966 (51 %) glioma cases and 1,716 (45 %) controls (Hepworth et al 2006). Cases were ascertained from multiple sources including hospital departments and cancer registries. The controls were randomly selected from general practioners' lists. Regular phone use gave OR = 0.9, 95 % CI = 0.8-1.1, increasing to OR = 1.2, 95 % CI = 1.02-1.5 for ipsilateral use but OR = 0.8, 95 % CI = 0.6-0.9 for contralateral use. Ipsilateral use for ≥ 10 years produced OR = 1.6, 95 % CI = 0.9-2.8, and contralateral OR = 0.8, 95 % CI = 0.4-1.4.

Schüz et al (2006) carried out a population-based case-control study in three regions of Germany, with incident cases of glioma and meningioma aged 30-69 years during 2000-2003. Controls were randomly drawn from population registries. In total, 366 (80 %) glioma cases, 381 (88 %) meningioma cases, and 1,494 (61 %) controls were interviewed. For glioma OR = 1.0, 95% CI = 0.7 - 1.3 and for meningioma OR = 0.8, 95% CI = 0.6 - 1.1 were obtained. However, among persons who had used cellular phones for ≥ 10 years increased risk was found for glioma; OR = 2.2, 95% CI = 0.9 - 5.1 but not for meningioma; OR = 1.1, 95% CI = 0.4 – 3.4. Among women they found OR = 2.0, 95 % CI = 1.1-3.5 for high-grade glioma for "regular" cell-phone use.

Summary results for mobile phone use and risk of glioma in Denmark, and parts of Finland, Norway, Sweden and United Kingdom have been published (Lahkola et al 2007). Of the included Interphone studies results had already been published from Sweden (Lönn et al 2005), Denmark (Christensen et al 2005) and UK (Hepworth et al 2006). The results were based on 2,530 eligible cases but only 1,521 (60%) participated. Regular mobile phone use gave OR = 0.8, 95 % CI = 0.7-0.9, but cumulative hours of use yielded OR = 1.006, 95 % CI = 1.002-1.010 per 100 hours. Ipsilateral mobile phone use for $\geq$ 10 years gave OR = 1.4, 95 % CI = 1.01-1.9, *p* trend = 0.04 and contralateral use OR = 1.0, 95 % CI = 0.7-1.4.

Use of mobile phones and risk of glioma and meningioma were published from Norway as part of the Interphone study (Klaeboe et al 2007). It included 289 (71 %) glioma cases, 207 (69 %) meningioma cases and 358 (69 %) controls. Significantly decreased OR = 0.6, 95 % CI = 0.4-0.9 was found for glioma and decreased OR = 0.8, 95 % CI = 0.5-1.1 for meningioma. For glioma 22 additional ORs were calculated using different exposure criteria as discussed above and all calculations yielded OR < 1.0, seven significantly so. Also for meningioma most ORs were < 1.0. Again these results indicate systematic bias in the study.

F. Meta-analysis

A meta-analysis of the risk for acoustic neuroma, glioma and meningioma was performed for mobile phone use with a latency period of 10 years or more (Hardell et al 2007). For acoustic neuroma studies by Lönn et al (2004), Christensen et al (2004) Schoemaker et al (2005) and Hardell et al (2006a) were included, all giving results for at least 10 years latency period or more. Overall OR = 1.3, 95 % CI = 0.6-2.8 was obtained increasing to OR = 2.4, 95 % CI = 1.1-5.3 for ipsilateral mobile phone use (Lönn et al 2004, Schoemaker et al 2005, Hardell et al 2006). For glioma OR = 1.2, 95 % CI = 0.8-1.9 was calculated (Lönn et al 2005, Christensen et al 2005, Hepworth et al 2006, Schüz et al 2006, Hardell et al 2006b, Lahkola et al 2007). Ipsilateral use yielded OR = 2.0, 95 % CI = 1.2-3.4 (Lönn et al 2005, Hepworth et al 2006, Hardell et al 2006b, Lahkola et al 2007). In total OR = 1.3, 95 % CI = 0.9-1.8 was found for meningioma (Lönn et al 2005, Christensen et al 2005, Schüz et al 2006, Hardell et al 2006a) increasing to OR = 1.7, 95 % CI = 0.99-3.1 for ipsilateral use (Lönn et al 2005, Hardell et al 2006b).

IV. Discussion

This review included 20 studies, two cohort studies and 18 case-control studies. We recently made a review on this topic and more details can be found in that publication (Hardell et al 2007). Only two studies have been published since then. Both were on acoustic neuroma (Klaeboe et al 2007, Schlehofer et al 2007). They were small with no cases with a latency period of at least 10 years. Furthermore, most ORs were < 1.0 indicating serious methodological problems in the studies.

So far most studies have had no or limited information on long-term users. No other studies than from the Hardell group has published results for use of cordless phones (Hardell et al 2006a,b). As we have discussed in our publications it is pertinent to include also such use in this type of studies. Cordless phones are an important source of exposure to microwaves and they are usually used for a longer time period on daily basis as compared with mobile phones. Thus, to exclude such use seems to underestimate the risk for brain tumors from use of wireless phones.

It should be noted that the Hardell group has included also use of cordless phones, and thus in the exposure assessment the "unexposed" cases and controls have not been exposed to either cordless or cellular phones. This is in contrast to the Interphone study where the "unexposed" may have been exposed to cordless phones of unknown amount.

Of the 18 case-control studies 11 gave results for $\geq$ 10 years use or latency period. However, most of the results were based on low numbers. Thus, it is necessary to get an overview if there is a consistent pattern of increased risk with longer latency period and to make a formal meta-analysis of these findings. Since brain tumours are a heterogenic group of tumours it is reasonable to separate the results for malignant and benign tumours, as has been done in the various studies.

The Danish cohort study (Johansen et al, 2001) is not very informative due to limits in study design, analysis and follow-up. Schüz et al. (2006) reported an update of this previous study on mobile phone subscribers in Denmark. Since this report has gained substantial media coverage as "proof" of no brain tumor risk from mobile phone use we will discuss the shortcomings of the study in more detail in the following.

The cohort was established for persons that some time during 1982–1995 were registered cellular telephone users and has now been followed against the Danish Cancer Registry until 2002, seven years more than in the previous study. Previously (Johansen et al, 2001) 9 persons with brain tumors had used GSM phones for > 3 years, and OR =1.2 was reported. Now, data were not provided for type of phone or years of use. Rather the calculation of latency was based on first year of registration.

During early 1980s almost all cellular telephones were used in cars with external antennae. These subjects were unexposed to electromagnetic fields (EMF). No information regarding such use is provided, and one may assume that such participants are now included as exposed although they were not. Over 200 000 (32 %) company subscribers were excluded from the cohort. These are the heaviest users and are billed 4.5 times more than the layman in Sweden. They started use the earliest, but were included in the “non-user” group, i.e., the general Danish population.

SIR among cellular telephone users was 1.21 for temporal glioma (Schüz et al 2006), a region most exposed to EMF, based on 54 persons and not on phone type or time of first use (latency period). No information regarding the ear used and correlation with tumor site was given. The expected numbers were based on the general population. Because a large part of the population uses mobile phones and/or cordless phones, and the latter use was not assessed at all in the study, there is no truly unexposed group for comparison. Risk of cancer was underestimated, e.g., in the group with first use $\geq$ 10 years, the associated risk for brain tumors was low (SIR =0.7, 95 % CI = 0.4- 0.95). Relying on private cellular network subscription as measure of mobile phone use has been questioned (Ahlbom et al 2004, Funch et al 1996).

There seems to be a “healthy worker” effect in the study because of the decreased overall cancer risk (SIR= 0.9, 95 % CI = 0.9-0.95). Of the subscribers 85 % were men and 15 % women. Certainly early mobile phone users are not socioeconomically representative of the whole Danish population, used for comparison. The cohort only included people > 18 years of age. We reported (Hardell et al 2004, 2006a,b) that cellular telephone use beginning before age 20 is associated with a higher risk of brain tumours than use starting after age 20.

The authors do not acknowledge the contribution by the telecom industry as cited in the first publication (Johansen et al 2001), i.e., TelemarkDanmarkMobil and Sonofom. Two of the authors are affiliated with the private International Epidemiology Institute, Rockville, MD, USA, which has contributed financially to the study. Where the International Epidemiology Institute gets its money from is not declared. In the application to the Danish National Mobile Phone Program, which funded part of the study, no mention of the involvement or payment of these two consultants was made, a fact that is now being set under question.

Regarding the case-control studies there seems to be a consistent pattern of an increased risk for acoustic neuroma using a 10-year latency period and considering ipsilateral exposure. It might be a “signal” tumour type for increased brain tumour risk from microwave exposure, since it is located in an anatomical area with high exposure during calls with cellular or cordless phones (Hardell et al, 2003). Christensen et al (2004) found no association using a ≥ 10 year latency period, but the result was based on only 2 cases. Interestingly, the tumours were significantly larger in the total group of regular mobile phone users.

In our study we found an increased risk also with shorter latency period than 10 years (Hardell et al 2006a). However, it is not known at what stage in the carcinogenesis microwaves act. An effect might exist at different stages both of promoter and initiator type. We conclude that the results on acoustic neuroma are consistent with an association with use of cellular phones using a latency period of ≥ 10 years.

Regarding meningioma no consistent pattern of an association was found, although ipsilateral exposure in the ≥ 10 years latency group increased the risk in the meta-analysis. For a definite conclusion longer follow-up studies are needed. We conclude that the results are not consistent with an association between use of mobile phones and meningioma.

Malignant brain tumours have been studied in 8 case-control studies. One study was register based and showed an increased risk associated with analogue phone use although the latency period seemed to be short (Auvinen et al 2002). The risk of glioma increased significantly per year of use. Five studies gave results for use of cell phone for 10 years or more. The pattern of an association was consistent in the different studies, except for the Danish study by Christensen et al (2005). In that study all 17 odds ratios for high-grade glioma were < 1.0 indicating systematic bias in assessment of exposure.

Our meta-analysis showed a significantly increased risk for ipsilateral use. We conclude that using $\geq$ 10 years latency period gives a consistent pattern of an association between use of mobile phones and glioma.

Regarding the Interphone studies the German part (Schüz et al 2006) was commented on by Morgan (2006) and these comments may also apply to the other Interphone studies. Morgan noted that the definition of a "regular" cell-phone user was so minimal that almost all "regular" cell-phone users would not be expected to be at risk, even if cell-phone use was found to create very high risks of glioma and meningioma. As for longer periods of "regular" cell-phone use, Schüz et al (2006) reported that only 14 percent of the glioma cases and 6 percent of the meningioma cases had used a cell phone for 5 years or more. For 10 years or more, the percentages were 3 percent and 1 percent, respectively. The authors replied that even long-term users in the study had barely more than 10 years of regular use and, in the beginning, were not heavy users; hence, they could not draw conclusions on heavy long-term use.

Methodological issues in the Interphone studies have been also discussed by Vrijhed et al (2006a,b). It was concluded that actual use of mobile phones was underestimated in light users and overestimated in heavy users. Random recall bias could lead to large underestimation in the risk of brain tumours associated with mobile phone use. According to the authors there was a selection bias in the Interphone study resulting in under selection of unexposed controls with decreasing risk at low to moderate exposure levels. Some of the Interphone studies had a low response rate, especially among controls giving potential selection bias.

A formal meta-analysis on mobile phone use and intracranial tumors was performed by Lahkola et al (2006). No data were given for $\geq$ 10 year latency period. Overall the risk increased for ipsilateral tumors, OR = 1.3, 95 % CI = 0.99-1.9 whereas no increased risk was found for contralateral tumors, OR = 1.0, 95 % CI = 0.8-1.4.

V. Conclusions

In summary we conclude that our review yielded a consistent pattern of an increased risk for acoustic neuroma and glioma after $\geq$ 10 years mobile phone use. We conclude that current standard for exposure to microwaves during mobile phone use is not safe for long-term brain tumor risk and needs to be revised.

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Table. Summary of 20 studies on the use of cellular telephones and brain tumour risk. For further details, see Hardell et al (2007). Odds ratio (OR), 95 % confidence interval (CI) and standardised incidence ratio (SIR) are given.

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al 1999, 2001 Sweden	1994-1996 Case-control	20-80 years	Brain tumours	217	OR 1.0 (0.7-1.4)	Analogue and digital cell phone use
				34	OR 1.1 (0.6-1.8)	Ipsilateral
				16	OR 1.2 (0.6-2.6)	> 10 year latency, analogue cell phone
Muscat et al 2000 USA	1994-1998 Case-control	18-80 years	Brain tumours	17	OR 0.7 (0.4-1.4)	Mean duration of use, 2.8 years
			Neuorepithelioma	35	OR 2.1 (0.9-4.7)	
Johansen et al 2001 Denmark	1982-1995 Cohort	0 to > 65 years	Brain tumours	20	SIR 1.3 (0.8-2.1)	Analogue and digital cell phone use
				9	SIR 1.2 (0.6-2.3)	≥ 3 years duration of digital subscription
Inskip et al 2001 USA	1994-1998 Case-control	≥ 18 years	Acoustic neuroma	5	OR 1.9 (0.6-5.9)	≥ 5 years of cell phone use
			Glioma	11	OR 0.6 (0.3-1.3)	
			Meningioma	6	OR 0.9 (0.3-2.7)	
Muscat et al 2002 USA	1997-1999 Case-control	≥ 18 years	Acoustic neuroma	11	OR 1.7 (0.5-5.1)	3-6 years of cell phone use
Auvinen et al 2002 Finland	1996 Case-control, register based	20-69 years	Glioma	119	OR 1.5 (1.0-2.4)	Analogue and digital cell phone ”ever” use
				40	OR 2.1 (1.3-3.4)	Analogue cell phone ”ever” used
				11	OR 2.4 (1.2-5.1)	Analogue cell phone use 1-2 years
				11	OR 2.0 (1.0-4.1)	Analogue cell phone use, >2 years
Lönn et al 2004 Sweden Interphone	1999-2002 Case-control	20-69 years	Acoustic neuroma	12	OR 1.8 (0.8-4.3)	≥10 years of cell phone use, result for either side of head
				12	OR 3.9 (1.6-9.5)	≥10 years of cell phone use on same side of head as tumour

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Christensen et al 2004 Denmark Interphone	2000-2002 Case-control	20-69 years	Acoustic neuroma	45	OR 0.9 (0.5-1.6)	Regular use
				2	OR 0.2 (0.04-1.1)	≥ 10 years cell phone use on same side of head as tumour. Significantly larger tumours among cellular phone users 1.66 cm^3 *versus* 1.39 cm^3, p=0.03.
Lönn et al 2005 Sweden Interphone	2000-2002 Case-control	20-69 years	Glioma	214	OR 0.8 (0.6-1.0)	Regular use
				15	OR 1.6 (0.8-3.4)	≥10 years since first "regular" cell phone use on same side of head as tumour
				11	OR 0.7 (0.3-1.5)	≥10 years since first "regular" cell phone use on opposite side of head as tumour.
			Meningioma	118	OR 0.7 (0.5-0.9)	Regular use
				5	OR 1.3 (0.5-3.9)	≥10 years since first "regular" cell phone use on same side of head as tumour
				3	OR 0.5 (0.1-1.7)	≥10 years since first "regular" cell phone use on opposite side of head as tumour.

Study	**Years Study Type**	**Age**	**Tumour type**	**No. of Cases**	**Odds ratio, 95 % confidence interval**	**Comments**
Schoemaker et al 2005 Denmark, Finland, Sweden, Norway, Scotland, England, Interphone	1999-2004 Case-control	18-69 years (variable)	Acoustic neuroma	360	OR 0.9 (0.7-1.1)	Regular use
				23	OR **1.8** (1.1-3.1)	≥ 10 lifetime years of cell phone use on same side of head as tumour
				12	OR 0.9 (0.5-1.8)	≥ 10 lifetime years of cell phone use on opposite side of head as tumour
Christensen et al 2005 Denmark Interphone	2000-2002 Case-control	20-69 years	Low-grade glioma	47	OR 1.1 (0.6-2.0)	Regular use
				9	OR 1.6 (0.4-6.1)	≥10 years since first regular use of cell phone
			High-grade glioma	59	OR 0.6 (0.4-0.9)	Regular use
				8	OR 0.5 (0.2-1.3)	≥10 years since first regular use of cell phone 17 odds ratios for high-grade glioma, all < 1.0, indicates systematic bias
			Meningioma	67	OR 0.8 (0.5-1.3)	Regular use
				6	OR 1.0 (0.3-3.2)	≥10 years since first regular use of cell phone
Hepworth et al 2006 UK Interphone	2000-2004 Case-control	18-69 years	Glioma	508	OR 0.9 (0.8-1.1)	Regular use
				NA	OR 1.6 (0.9-2.8)	≥10 years of cell phone use on same side of head as tumour.
				NA	OR 0.8 (0.4-1.4)	>10 years of cell phone use on opposite side of head as tumour.

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Schüz et al 2006 Germany Interphone	2000-2003 Case-control	30-59 years	Glioma	138	OR 1.0 (0.7-1.3)	Regular use
				12	OR 2.2 (0.9-5.1)	≥ 10 years since first regular use of cell phone
				30	OR **2.0** (1.1-3.5)	Female regular use of cell phone
			Meningioma	104	OR 0.8 (0.6-1.1)	Regular use
				5	OR 1.1 (0.4-3.4)	≥ 10 years since first regular use of cell phone

Study	**Years Study Type**	**Age**	**Tumour type**	**No. of Cases**	**Odds ratio, 95 % confidence interval**	**Comments**
Hardell et al 2006a Sweden	1997-2003 Case-control	20-80 years	Acoustic neuroma	130	OR **1.7** (1.2-2.3)	> 1 year latency of cell phone use
				20	OR **2.9** (1.6-5.5)	> 10 years latency of cell phone use
				10	OR **3.5** (1.5-7.8)	> 10 years of ipsilateral cell phone use
				4	OR 1.0 (0.3-2.9)	> 10 years latency of cordless phone use
				3	OR 3.1 (0.8-12)	> 10 years latency of ipsilateral cordless phone use
			Meningioma	347	OR 1.1 (0.9-1.3)	> 1 year latency of cell phone use
				38	OR 1.5 (0.98-2.4)	> 10 years latency of cell phone use
				15	OR 2.0 (0.98-3.9)	> 10 years latency of ipsilateral cell phone use
				23	OR 1.6 (0.9-2.8)	> 10 years latency of cordless phone use
				9	OR **3.2** (1.2-8.4)	> 10 years latency of ipsilateral cordless phone use
Hardell et al 2006b Sweden	1997-2003 Case-control	20-80 years	Glioma, high-grade	281	OR **1.4** (1.1-1.8)	> 1 year latency of cell phone use
				71	OR **3.1** (2.0-4.6)	> 10 years latency of cell phone use
				39	OR **5.4** (3.0-9.6)	> 10 years latency of ipsilateral cell phone use
				23	OR **2.2** (1.3-3.9)	> 10 years of cordless phone use
				10	OR **4.7** (1.8-13)	> 10 years latency of ipsilateral cordless phone use
			Glioma, low-grade	65	OR 1.4 (0.9-2.3)	> 1 year latency of cell phone use
				7	OR 1.5 (0.6-3.8)	> 10 years latency of cell phone use
				2	OR 1.2 (0.3-5.8)	> 10 years latency of ipsilateral cell phone use
				5	OR 1.6 (0.5-4.6)	> 10 years latency of cordless phone use
				3	OR 3.2 (0.6-16)	> 10 years latency of ipsilateral cordless phone use

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Takebayashi et al 2006 Tokyo Interphone	2000-2004 Case-control	30-69 years	Acoustic neuroma	51	OR 0.7 (0.4-1.2)	Regular use
				4	OR 0.8 (0.2-2.7)	Length of use > 8 years
				20	OR 0.9 (0.5-1.6)	Ipsilateral use
Schüz et al 2006 Denmark	1982-2002 Cohort	>18 years	Glioma	257	SIR 1.0 (0.9-1.1)	420 095 telephone subscribers
			Meningioma	68	SIR 0.9 (0.7-1.1)	
			Nerve sheat tumors	32	SIR 0.7 (0.5-1.0)	
			Brain and nervous system	28	SIR 0.7 (0.4-0.95)	Latency ≥ 10 years
Lahkola et al 2007 Denmark, Norway, Finland, Sweden, UK Interphone	September 2000-February 2004 (differed between countries) Case-control	20-69 years (Nordic countries), 18-59 years (UK)	Glioma	867	OR 0.8 (0.7-0.9)	Regular use
				77	OR 1.4 (1.01-1.9)	Ipsilateral mobile phone use, ≥10 years since first use, *p* for trend = 0.04
Klaeboe et al 2007 Norway Interphone	2001-2002 Case-control	19-69 years	Glioma	161	OR 0.6 (0.4-0.9)	Regular use
			Meningioma	111	OR 0.8 (0.5-1.1)	
Schlehofer et al 2007 Germany Interphone	2000-2003 Case-control	30-69 years	Acoustic neuroma	29	OR 0.7 (0.4-1.2)	Regular use

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SECTION 10 – Part 2

EVIDENCE FOR BRAIN TUMORS

(EPIDMIOLOGICAL)

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Prepared for the BioInitiative Working Group
July 2007

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I. INTRODUCTION

Primary central nervous system (CNS) tumors are a heterogeneous group of benign and malignant neoplasms localized in the brain, the spinal cord and their coverings. They differ in histological type, tissue of origin, anatomic site, growth pattern, age distribution, sex ratio, clinical appearance and many other features including molecular neuropathological markers. These features are not independent but little is known about the etiology of these tumors and the reason for the observed epidemiological patterns. The rapidly developing field of molecular neuropathology may provide clues to solve these problems in the future.

Brain tumors, accounting for the majority of CNS tumors, are rare. Annually about 36,000 36000 new cases are diagnosed in the US and about 180,000 180000 world-wide. The age distribution has two peaks: incidence is about 35 cases per million per year below 10 years of age (which is mainly due to tumors originating from mesodermal and embryonic tissues, medulloblastoma and astrocytoma of the juvenile pilocytic type), and after age 15 there is a steady increase of incidence with increasing age reaching its second peak of about 200 cases per million per year at an age around 75 years. The burden of CNS cancers is distinctly higher in children making up around 20% of all childhood malignancies, while in adults less than 2% of all cancers are primary brain cancers.

There are some rare cases of inherited cancer syndromes (e.g. von Hippel-Lindau disease, Li-Fraumeni syndrome) that are related to brain tumor risk, accounting for a small fraction of cases. Except for therapeutic x-rays no environmental or lifestyle life-stile factor has unequivocally been established as risk factor for brain tumors. Non-whites Non whites seem to have lower risk, and incidence tends to be higher with increasing socio-economic status. However, because of the rather advanced age of 75 of peak incidence, such differences may partly be due to differences in life-expectancy. During the last decades some types of brain tumors show a steady increase of a few percent per year, which might to some extent be related to the introduction of computed tomography and other high-resolution neuroimaging methods.

Since the report of Wertheimer and Leeper in 1979 of an increased incidence of brain tumors in children living in homes with an expected higher exposure to power-frequency electric and magnetic fields, exposure to electromagnetic fields have become an area of interest in the study of factors affecting brain tumor risk.

This review focuses on the radio frequency (RF) part of the electromagnetic spectrum (3 kHz to 300 GHz). However, because the epidemiology of mobile phone use is covered in another section, it will be restricted to RF exposure conditions other than microwaves from mobile phone use. Exposure to ELF magnetic fields and childhood brain tumors is covered in the chapter about childhood cancers.

II. Material and Methods

Published articles of relevant studies restricted to the last 20 years were obtained by searching PubMed using the following terms:
("radio frequency" OR electromagnetic* OR microwaves) AND ("brain cancer" OR brain tumor* OR "CNS cancer" OR CNS tumor* OR glioma* OR meningioma* OR neuroma*) NOT ("power frequency" OR "low frequency") AND epidemiology

The search resulted in 101 hits. After removing reviews and animal or in vitro studies as well as studies of mobile phone use, 8 articles remained. A hand search in review papers (Krewski et al. 2001; Elwood 2003; Ahlbom et al. 2004; Kundi et al. 2004) and reference lists of the articles found in PubMed revealed another 7 papers; hence the final body of evidence consists of 15 studies of exposure to various types of RF fields.

Of the 15 studies 8 were cohort studies, 3 case-control studies and 4 of an ecological type. The majority (11) were occupational studies, two studies investigated children, and one ecological study investigated adults and one study both, adults and children.

III. Epidemiological studies of RF fields and brain tumors

Table 1 gives an overview of the 15 studies obtained by the literature search with respect to study type, assessment of exposure and outcome, confounders considered and matching variables used, number of cases included and selection method of study participants. Results are summarized in Table 2.

In the following paragraphs each study is briefly discussed with respect to its strengths and weaknesses.

A. Thomas et al. 1987

This case-control study included 435 deaths from brain or CNS tumors and 386 deaths from other causes as controls. Only adult males were included. Basis of data collection on occupational history were interview with next-of-kin. Two methods of classification were used: one method assigned subjects to one of three categories (never exposed to RF/ever exposed to RF in an electrical or electronics job/ever exposed to RF but not in an electrical or electronics job), the other method consisted in a classification of each job by an industrial hygienist hyginiest for presumed exposure to RF, soldering fumes, and lead. Both methods revealed significantly increased brain tumor risks of presumed occupational exposure to RF fields. This increase was due to an association in electronics and electrical jobs with astrocytic tumors as the predominant outcome associated with employment in these categories. In addition a significant increase of brain tumor risk was found for increasing duration of exposure.

Although relying on information of next-of-kin could be a source of misclassification, one strength of this study is it’s its relying on occupational history only that could be assumed to be more accurate than recall of exposure to various agents. The two methods of classification led to almost the same results, which lends support to the hypothesis that indeed exposure in electrical and electronics jobs is associated with an increased brain tumor risk. Due to the strong relationship between RF exposure and exposure to lead, solvents or soldering fumes in these jobs, it is not possible to separate effects of these exposures. However, analysis of exposure to lead did not show a consistent relationship with brain tumor risk, indicating that it may not confound the relationship to RF exposure.

Because this study is of dead cases only it is likely over-representing high grade brain tumors that may not all be associated with exposure which leads to an effect dilution. Exposure misclassification, if it is non-differential in cases and controls, also tends to reduce effect estimates.

A weakness of this study is obviously its lack of an exposure indicator other than the occupational category. While there is no doubt that in these jobs some exposure to RF fields occur quite regularly, specific characteristics including frequency ranges, modulation, intensity, duration and distance from the source vary considerably. Overall the study (as well as two earlier ones outside the search window: Lin et al. 1985 and Milham 1985) are sufficient to formulate a research hypothesis that can be tested in appropriately designed subsequent investigations. Unfortunately such studies have never been conducted.

B. Milham 1988

In this cohort study of 67,829 amateur radio operators holding a license within 1/1979 to 6/1984 in Washington and California 29 brain tumor deaths occurred during the follow up period with 21 expected.

It should be noted that there was a substantial and statistically significant lower number of overall deaths of less than three quarters of deaths expected from country mortality rates. This could be due to both a ‘healthy-worker’ effect as well as an effect of socio-economic status. In lieu of computing standardized mortality ratios (SMR) it may be instructive to look at the proportional mortality rates in the reference population and the amateur radio operators: 0.6% of all deaths are expected to be due to brain tumors in the reference population while in amateur radio operators twice as many occurred (1.2%). Whether or not this is an indication of an increased brain tumor risk due to RF exposure is difficult to assess. First of all this study is a register only investigation and no information on intensity, frequency and duration of engagement in amateur radio operations are available. In a later analysis the author reported about results using a proxy of intensity and duration of exposure: the license class. In this analysis indications of an increase of risk with increasing license class were obtained.
This study could and should have started off a thorough follow up of amateur radio operators and nested case-control studies to address the problem of potential confounders and to narrow down the conditions that may be responsible for the increased mortality from some cancers. It is another loose end that leaves us without a clear message.

Although no risk factor for brain cancer except therapeutic ionizing radiation is known, there are some indications that risk increases with social class. The reason for this association is unknown but life-style factors may play a role as well as concomitant causes of death that could lead to a spurious reduction of risk in lower class populations because brain tumors have their peak close to life-expectancy.

C. Selvin et al. 1992

The objective of this investigation was not primarily to study the relationship between RF exposure and childhood cancer but to address the general problem of how to assess disease incidence or mortality in relation to a point source. As the point source the Sutro Tower in San Francisco, the only microwaves emitting tower in this county, was chosen. A total of 35 brain tumor deaths occurred among 50,686 white individuals at risk aged less than 21 in the years 1973-88 in an area of approximately 6 km around the tower. The exact location of residence could not be obtained; therefore each case was located in the center of the census tract. Different methods of analysis were applied to assess a potential relationship between distance from the tower and brain tumor risk. Relative risk for brain tumors for a distance less than 3.5 km from Sutro Tower compared to more than 3.5 km was 1.162 and not significant.
The study explored different methodological procedures and has its merits from a methodological point of view. However, it starts from the wrong assumption: that distance to a point source is a valid proxy for intensity of exposure. Under ideal conditions of spherical symmetry of an emission this assumption holds, however, there are almost no real life situations where this assumption is sufficiently close to actual exposure levels. And it is definitely not true for the Sutro Tower. Radiations from the antennae are directed towards the horizon and the complex pattern of emission with main and side lobes results in a complex pattern of RF exposure at ground level. Furthermore, the area is topographically structured with hills and valleys such that areas of high exposure at the vertices are in close proximity to areas of low exposure at the shadowed side downhill.

Studying the relationship between a point source and disease is not only difficult due to the complex relationship between distance and exposure but also because of the fact that humans are not stable at a certain location. This is of greater importance for adults who may commute from and to work places and have generally a greater radius of activity as compared to children. Nevertheless, there is at least a high chance of one long-lasting stable location that is when people sleep in their beds. Therefore, studies in relation to a point source should attempt to assess exposure at the location of the bed. Because the objective of this study was not the assessment of a potential brain tumor risk but the application of methods for the analysis of spatial data, no attempts were made to measure actual exposure.

D. Tynes et al. 1992

In this study information on occupations obtained for all Norwegians every 10 years was used to assess cancer incidence in relation to job titles. In 1960 37,945 male workers were identified that had jobs with possible exposure to EMFs and among these 3,017 with possible RF exposure. Overall 119 brain tumor cases were found in the cancer registry between 1961 and 1985. Of these cases 6 occurred in the subgroup of workers possibly exposed to RF fields. The overall expected number of brain tumor cases was 109 and 12 for the subgroup with possible RF exposure. Hence no increased brain tumor risk could be detected.

Despite the long follow-up period of 25 years with an accumulated number of 65,500 person-years the expected number of brain tumors diagnosed during that period is too low to detect a moderately elevated risk of 1.3 to 1.5.

As mentioned above, all studies solely relying on job titles lead to exposure misclassification and, therefore, to a dilution of risk. For dichotomous exposure variables (exposed/not exposed) and assuming a negligibly small proportion of exposed in the reference population standardized incidence ratios (SIR) are biased by a factor (1+f*(SIR-1))/SIR, if f denotes the fraction of true exposed and SIR is the true incidence ratio. Hence a true SIR of 2.0 is reduced to 1.5 if only 50% in the cohort are actually exposed. The observed SIR is further reduced if the assumption of a negligible fraction of exposed in the reference population is wrong. In this case the bias factor given above is further divided by (1+g*(SIR-1)), where g is the fraction of exposed in the general population.

While a cohort study that is based on registry data has the advantage of independence from recall errors and selection bias due to possible differential participation, it has the disadvantage that registry data are generally insufficient to provide reliable exposure indicators. While no association with brain tumors could be detected in this study it revealed an increased number of leukemia cases in occupations with possible RF exposure. This could be due to the higher incidence of leukemia or to a stronger association or to different latency periods and various other reasons including chance.

E. Grayson 1996

In this case-control study nested within approx. 880,000 US Air Force personnel with at least one years of service during the study period of 1970-89 primary malignant brain tumor cases were ascertained by screening hospital discharge records. The study included only males and only as long as they were on Air Force records. From 246 cases detected 16 were dropped due to incomplete or ambiguous data. For each case four controls were randomly selected from the case's risk set matching it exactly on year of birth and race. Controls who were diagnosed with diseases that may be associated with EMF exposure (leukemia, breast cancer, malignant melanoma) were excluded from the risk set.

One strength of this study is the detailed job history filed for each cohort member that could be used for retrospective exposure assessment. Furthermore, Air Force files contained detailed data from personal dosímetry on ionizing radiation for the different posts and jobs. Classification of RF field exposure was based on a detailed job exposure matrix with over 1,950 entries, indexing 552 different job titles. One source of classification was recorded events of exposure to RF fields above 100 W/m2. By this method probable exposure was assigned if for a job such events were recorded in the past as well as for closely related jobs. Possible exposure was assigned for jobs that required operation of RF emitters but without recorded overexposure.

A further strength is the thorough consideration of possible confounders. Because of the possible relationship of brain tumor risk with socio-economic status (SES), military rank was used as a surrogate for SES and included in the analysis as well as ionizing radiation exposure that has previously been shown to increase brain tumor risk.

Exposure to RF fields was associated with a moderate but statistically significant increased risk of OR=1.39. Investigation of duration of exposure was compromised by an ambiguity introduced by the calculation of an exposure score as the product of exposure and months. Nevertheless, for those ever exposed there were indications of an increasing risk with increasing exposure duration.

A weakness of this investigation is its incomplete follow-up of cohort members. This could have resulted in an underestimation of the true risk. Leaving the Air Force could have been more likely in those exposed to RF fields and developing a brain tumor. Some malignant brain tumors have early signs that could be incompatible with the Air Force job especially if involving operation of RF equipment (like seizures, severe headaches, somnolence, and absences). Because the study did not involve personal contact it is free of other selection biases.

F. Szmigielski 1996

In this military cohort study of cancer morbidity Polish military career personnel was assessed for occupational exposure to RF fields based on service records. The study covered 15 years (1971-85) including approx. 128,000 persons per year. Expected rates for 12 cancer types were calculated based on the age specific morbidity in those classified as unexposed.
For brain and nervous system tumors a significantly increased ratio of observed to expected (OER=1.91) was found. Other malignancies with significantly increased incidence in exposed were: esophageal and stomach cancers, colorectal cancers, melanoma, and leukemia/lymphoma.

One strength of this study is its substantial size with almost 2 million person-years of follow-up. Furthermore, accurate military records on job assignment and on exposure from military safety groups gives a unique opportunity to assess long-term exposure effects based on already filed data.

Some important data are missing because they were military classified information that could not be provided in the paper. This includes the exact number of cases of the different neoplasms. However, from the data presented an observed number of brain tumors of about 46 can be calculated.

The study has been criticized for an alleged bias because more information on risk factors was available for cancer cases. It is true that military medical boards collected data for cases such as life style factors and exposure to possible carcinogens during service, however, at no stage this information entered the analysis. Therefore, this criticism is unfounded. Such information could have been utilized within a nested case-control study applying the same methods of assessment of risk factors for controls as has been done for cases. Because some findings, such as the increased risk for esophagus/stomach cancer, that are rarely reported in relation to

RF exposure warrant further study, such a nested case-control approach is recommended. It could, albeit with some difficulties, even be successfully conducted retrospectively.

G. Hocking et al. 1996

In an ecological study cancer incidence and mortality in nine municipalities of northern Sydney during 1972-90 three of which surround three TV towers were assessed. Population size in the three municipalities located within a radius of approximately approx. 4 km around the TV towers amounts to 135,000 while population size in the six municipalities further away was 450,000. High-power transmission commenced in 1956, an additional 100 kW transmission started in 1965 and another 300 kV broadcast in 1980. Carrier frequencies varied between 63 and 533 MHz for TV broadcasting and was around 100 MHz for FM radio broadcast.

During the study period 740 primary malignant brain tumors were diagnosed in adults and 64 in children, 606 deaths due to brain cancer occurred in adults and 30 in children. While incidence of lymphatic leukemia was significantly higher in adults as well as in children inhabiting the three municipalities surrounding the transmission towers compared to the six districts further away, brain tumor incidence was not significantly elevated (RR=0.89 in adults and 1.10 in children).

As has been stated above, distance from a transmitter is a poor proxy for exposure. Some measurements done in the study area obtained levels much lower than those calculated from the emission power and antenna gain. Several factors are responsible for this effect: multiple reflections, attenuation by buildings and vegetation, ground undulations, non-coincidence of maxima for the different signals as well as complex radiation characteristics of the broadcast antennae.

The exact location of the residence of cases could not be provided which reduces the potential of the study to relate incidences to measurements or calculations of RF fields. Authors discussed some potential sources of bias such as migration and other exposures in the different regions. However, the most important disadvantage in such studies is that individual risk factors cannot be adjusted for. Both spurious positive as well as false negative results can be obtained by disregarding such individual variables.

H. Tynes et al. 1996

In a historical cohort study 2,619 Norwegian female radio and telegraph operators certified between 1920 and 1980 were followed from 1961 through 1991 for entries in the cancer registry. During this period a total of 140 cases of cancer occurred which are about 20% more than expected from the Norwegian population. Among these were 5 brain tumor cases closely matching the number expected.

An excess for breast cancer was found in this study that may be related to a combination of RF field exposure and night work. For other cancers including brain cancer numbers of cases were too low to address exposure risk.

In this very thoroughly conducted study including a nested case-control approach for breast cancer, measurements at historical transmitters on ships, comparison with women at other jobs on sea, brain tumors were not distinctly higher than expected from the reference population. However, because of the limited cohort size a moderately increased risk cannot be excluded.

I. Dolk et al. 1997a

This ecological small area study of cancer incidence 1974-86 near the Sutton Coldfield TV/radio transmitter at the northern edge of the city of Birmingham (England) was initiated by an unconfirmed report of a ‘cluster’ of leukemias and lymphomas. The transmitter came into service in 1949. Transmission at 1 megawatt (effective radiated power erp) began in 1964, at 3 MW in 1969, and at 4 MW in 1982. The tower has a height of 240 m with no big hills in the surrounding area. The study area was defined by a circle of 10 km radius centered at the transmitter. The population within this area was about 408,000. All cancers, excluding non-melanoma skin cancer, were considered focusing on hematopoietic and lymphatic cancers, brain and nervous system cancers, eye cancer, and male breast cancer. Childhood cancers were restricted to all cancers and all leukemias.

In the study area a small but significant excess of all cancers was observed in adults. All leukemias and non-Hodgkin’s lymphoma were particularly elevated and incidence within 2 to

4 km from the tower was about 30% higher than expected. Brain tumors were only analyzed for distances of within 2 km and the whole study area. Within 2 km an increased OER of 1.29 for all brain tumors and 1.31 for malignant brain tumors was calculated based on 17 and 12 cases, respectively.

Also this investigation suffers from using distance from the tower as proxy for intensity of exposure. The wrong assumption that exposure decreases with increasing distance invalidates the statistical trend test applied. Measurements conducted in the study area revealed the poor relationship with distance but without consequences on the evaluation of the data. Overall the study is consistent with a moderately increased risk of hematopoietic and lymphatic cancers as well as some other cancers including brain cancer in the vicinity of high-power transmitters that, if related to RF fields, must be substantially higher for actual exposure.

The Sutton Coldfield study was later continued (Cooper & Saunders 2001) to cover the period 1987-94. The study revealed, compared to the earlier period, an almost unchanged increase of leukemias and non-Hodgkin's lymphoma in adults and a slight increase in children.

J. Dolk et al. 1997b

Because the Sutton Coldfield study was triggered by a cluster report and to provide independent test of hypotheses arising from that study, similar methods as applied in the previous study were used to study all high-power TV/radio transmitters (≥ 500 kW ERP) in Great Britain. In adults leukemias, bladder cancer, and skin melanoma, and in children, leukemias and brain tumors were studied. The study period was 1974-86 for England and somewhat shorter in Wales and Scotland.

Although population density around transmitters was not always as high as in the case of the Sutton Coldfield tower, with an average population density of only about one third of that around Sutton Coldfield tower within 2 km from the towers, in the most important range of 2 to 4 km from the transmitters, where in many cases the maximum of radiated RF at ground level is reached, population density was similar. The study of all high-power transmitters essentially corroborated the findings for adult leukemias with an increase of incidence between 10 and 50% in the distance band of 2 to 4 km from the transmitters for the different transmitter types. Most of these increased incidences were statistically significant.

For children only the incidence in the whole study area and within a distance of 2 km was calculated, which is unfortunate because the area close to the towers is sparsely populated and exposure is low. Number of brain tumors in children was slightly above expectation (244 observed and 231 expected).

In contrast to the interpretation by the authors, the study of all high power transmitters essentially replicated and supported the findings of an excess incidence of leukemias in relation to RF emission from TV/radio towers. Because the different heights and radiation characteristics of the transmitters result in different exposure patterns at ground level, the consistent increase in an area that is likely close to the maximum of exposure supports the hypothesis of an association.

K. Lagorio et al. 1997

A mortality study of a cohort of 481 female plastic-ware workers employed between 1962-92 in an Italian plant, 302 of which were engaged in the sealing department with exposure to RF fields, was reported by Lagorio et al. (1997). For RF-sealers 6,772 person-years of follow-up were accumulated and overall 9 deaths occurred, 6 of which were from malignant neoplasms (which are twice as many as expected from comparison with the local reference population). In the 31 years only one brain cancer occurred but only 0.1 were expected.

Although the small size of the cohort and the potential exposure to other agents except RF fields such as solvents and vinyl chloride prohibit far reaching conclusion, much more of such thorough follow-up studies of exposed cohorts are needed to accumulate a body of evidence that can provide a useful basis for analysis.

L. Finkelstein 1998

A preliminary study intended to form the basis for an assessment of cancer risks associated with handheld radar devices was conducted among a cohort of 20,601 male Ontario police officers. The retrospective follow up covered the period of 1964-95. By linkage with the cancer registry and mortality database 650 cases of cancer were detected.

Testicular cancer and melanoma showed an excess incidence while overall cancer incidence was reduces as expected from a working cohort. Overall 16 cases of primary malignant brain tumors occurred which are slightly less than expected.

The author had difficulties to build up a proper cohort because some departments refused to participate and others couldn’t spare the time to provide lists of all officers employed during the target period. Furthermore, while cancer sites of primary interest showed actually an increased incidence calling for a nested case-control approach, this study was never conducted due to lack of interest and support of the authorities.

M. Morgan et al. 2000

In an occupational cohort study all US Motorola employees with at least 6 months cumulative employment and at least 1 day of employment in the period 1976-96 were included. A total of 195,775 workers contributing about 2,7 million person-years were available for the study. The cohort was compared to the SSA Master Mortality File and the National Death Index to obtain vital status. Death certificates were obtained by states’ vital statistics offices and company records. Exposure was assessed by expert opinion. Four RF exposure groups were defined with increasing level of estimated RF exposure. Only about 5% of the total cohort was classified as highly exposed and more than 70% with only background exposure. Neither private nor occupational mobile phone use was included.

Overall 6,296 deaths occurred in the cohort in 21 years, which were only two thirds of deaths expected from mortality data of the four countries where most Motorola facilities are located. This reduction is too pronounced to be solely due to a healthy worker effect, other factors such as higher SES must have contributed, an interpretation supported by the substantial reduction of mortality from all life-style associated causes of death. Internal comparisons were done for mortality from brain cancer and hematopoietic and lymphatic cancers. Brain tumor mortality was slightly but insignificantly elevated in high and moderately high exposed workers as compared to those with no or low RF exposure.

This study of a huge cohort demonstrates the limitations of such a study design. The majority of the cohort (58%) consisted of retired or terminated workers that may or may not accumulate further RF exposure at other companies. Furthermore, it can be assumed that

Motorola employees were among the first that used mobile phones at the workplace and privately. Neglecting mobile phone use may diminish the gradient of exposures between occupational groups studied. It would have been better to conduct nested case-control studies instead of using internal comparison that may be compromised by mobility bias, exposure misclassification and other sources of bias.

N. Groves et al. 2002

In this military cohort study of 40,581 men followed from the year of graduation (1950-1954) from Navy technical schools through 1997, known as the Korean War Veterans study, groups of sailors with imputed difference in likelihood and amount of exposure to radar waves were compared with respect to mortality. The original study, with a follow up through 1974, (Robinette et al. 1980) reported increased risks of cancer of the hematopoietic and lymphatic system, of the lung and digestive system for the high exposure group but was handicapped by the lack of information on date of birth of the cohort members. For the extended follow up study many missing birth dates were found in the Veterans Administration Master Index. Nevertheless, birth date remained unknown for over 8% of the cohort. Based on expert opinion low RF exposure was assigned to job classifications of radioman, radarman, and aviation electrician’s mate, high exposure stratum included men with job classifications of electronics technician, aviation electronics technician, and fire control technician.
By matching against the Social Security Administration’s Death Master File and the National Death Index 8,393 deceased subjects were identified through 1997. This number is substantially and significantly lower as expected from the male white US population. A healthy soldier effect may have been responsible for a lower mortality rate in the 1950ies but cannot explain the reduced mortality after 40 years. It has not been reported how long the cohort members stayed in service nor were life-style factors investigated; however, of more than 40% of the cohort no social security number could be obtained suggesting possible under-estimation of deaths.

Comparison of high- with low-exposure groups revealed significantly lower mortality from life-style associated causes of death (lung cancer, vascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, liver cirrhosis) and significantly higher mortality from all leukemias and external causes of death. Increased mortality from leukemias was found in all high exposure groups but the most pronounced increase was observed in aviation electronics technicians. Brain cancer was less frequent in all high exposure groups compared to the low exposure category.

The long period of follow up of this large cohort with start of follow up almost at the same time (1950-54) and at a time when exposure commenced is a great advantage of this investigation. However, there are a number of shortcomings: follow up was possibly incomplete by unknown social security number of a substantial proportion of the cohort; almost half of all deaths in the first 20 years were from external causes which could have obscured an effect of exposure; duration and intensity of exposure is unknown as well as potential exposure after leaving the Navy; classification into low and high exposure groups may introduce substantial misclassification. In the earlier report, inspection of Navy records for a sample from the high exposure group revealed that 24% had no exposure to radar waves at all.

Concerning brain tumors, assuming an effect of radar exposure on growth rate, exposure during the Korean War and no exposure afterwards would be expected to result in only a slightly increased risk during a period of about 10 years after the war. Sailors were about 20 to 25 years at that time. The fraction with an already initiated brain tumor during this age range is estimated to be less than 3 in 100,000 per year. Increase of growth rate even if substantial cannot result in an effect observable in a cohort of that size. If radar exposure increases the likelihood of malignant transformation this could increase the incidence during a time window of 10 to 20 years after the exposure period. Results of the Israeli study of x-ray treated tinea capitis (Sadetzki et al. 2005) suggest an even longer latency, however, risk decreased with increasing age at first exposure to x-rays. In addition, for malignant brain tumors there is a less pronounced relationship to ionizing radiation, and a higher risk was observed for meningioma that were not investigated in the Korean War Veterans study. Taking the data on ionizing radiation as a guiding principle for brain tumor initiation, radar exposure of sailors during their twenties might result in an increase of brain tumor mortality of about 10 to 15%, i.e. a maximum of 8 additional cases among 20,000. Considering the biases of the study such a low risk is easily obscured. Hence neither tumor promotion nor initiation may be detected in this study even if there is an increased risk. Because of the mentioned limitation to a certain time window with possibly increased incidence due to exposures during service in the Korean War, it would have been instructive to compute Kaplan-Meier estimates for cumulative brain tumor mortality.

N. Berg et al. 2006

In the German part of the Interphone study special attention was paid to occupational history and exposure to RF fields at workplaces. Incident meningioma (n=381, response rate 88%) and glioma cases (n=366, response rate 80%) aged 30-69 years were selected from four neurological clinics. Overall 1,535 (participation rate 63%) were randomly selected from population registries matched to the cases by sex, age, and region. Most cases were interviewed during their stay in hospitals, controls were interviewed at home. The interview contained several screening questions about occupations that are probably associated with RF exposure. If any of these screening questions were marked additional questions were asked about the job. Based on the literature and the evaluation by two industrial hygienists a classification into the following categories was performed: no RF exposure/not probably RF exposed/probably ER exposed/highly RF exposed. In total about 13% (299 cases and controls) were classified with at least possible RF exposure at the workplace. Analyses were adjusted for region, sex, age, SES, urban/rural residence, ionizing radiation exposure in the head/neck region. Mobile phone use was not considered as a confounder.
While overall RF exposure at workplaces showed no increased odds-ratios, high exposure and especially for durations of 10 years or more resulted in elevated risk estimates that were, however, not significant. This result was similar for meningioma (OR=1.55 for high exposure for 10 years or more) and glioma (OR=1.39).

The study tried to assess potential workplace exposure as precisely as possible in a personal interview, but still misclassification may have occurred especially in the probable and not probable categories while the high exposure group is likely to have had at least occasionally above average RF exposure. Odds ratios are in the range expected if exposure results in a substantial increase of growth rate. The small number of highly and long-term exposed cases (13 glioma and 6 meningioma) prohibit, however, far reaching conclusions.

IV. Evaluation of Evidence

Due to the varying endpoints, methods used and populations included and the small number of studies a formal meta-analysis is not possible. The following figure shows the results detailed in Table 2 in an easily comprehendible way.

Only few studies found clear indications of an association between RF exposure and brain tumors: one cohort study (Szmigielski 1996) and two case-control studies (Thomas et al. 1987, Grayson 1996). None of the ecological studies demonstrated a tendency for an increased risk in the vicinity of RF transmitters.

The discussion of the 15 published investigations revealed shortcomings in all studies. The greatest problem was encountered in the difficulties to reliably assess actual exposure. Even if we don't know the relevant aspect of the exposure, if any, that is responsible for an increased risk, the type, duration and amount of exposure must be determined in order to use the studies in derivations of exposure standards. None of the studies included a useful quantitative indicator of intensity of exposure and even duration of exposure was rarely addressed. Concerning type of exposure only quite crude and broad categories were used.

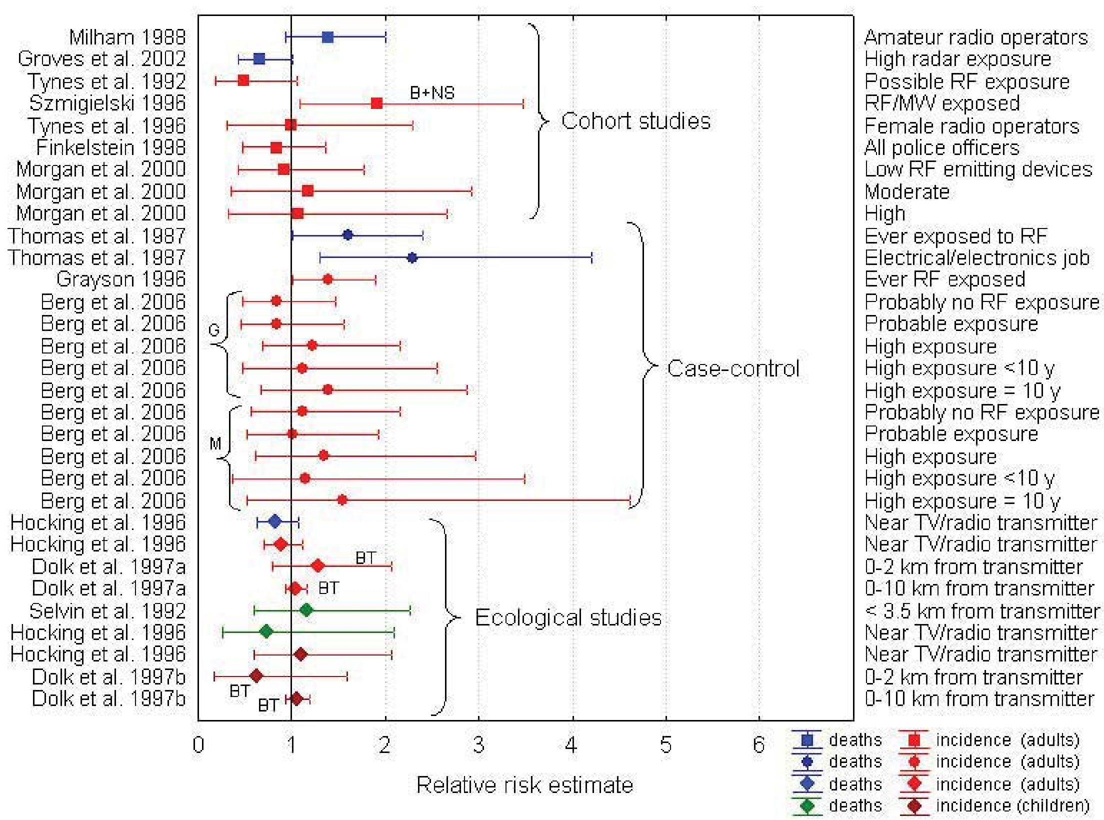

Fig. 1: Estimates of relative risk (and 95% confidence intervals) of various RF exposures with respect to brain tumors (B+NS…brain and nervous system tumors, BT…brain tumors, M…menigioma, G…glioma; all others primary malignant brain tumors)

In ecological studies, although for the studied population the exposure - despite considerable variations in time - is similar with respect to carrier frequency, modulation etc. it is quite different between various types of transmitters and hence results are not easily generalized.

Considering the discussion of the different investigations and the fact that most biases encountered tend to dilute a potential risk, the compiled evidence from occupational cohorts is compatible with a moderately increased risk of RF exposure. Because of the lack of actual measurements but observing that exposure above guideline levels must have been a rare event a precautionary approach must result in a reduction of occupational exposure levels and organizational measures to avoid over-exposure. Although brain tumors are rare and the population attributable risk is low (assuming 13% of adults being occupationally exposed to RF fields as inferred from Berg et al. 2006, and assuming a relative risk of 1.3, about 4% of brain tumors can be attributed to RF exposure, i.e. 1,350 cases per years in the US).

V. EVALUATION OF CANCER-RELATED ENDPOINTS (RF EXPOSURE)

A. Assessment of Epidemiological Evidence by IEEE (C95.1 Revision)

In their 2006 revision of the standard C95.1 IEEE has assessed the evidence from epidemiology for cancer related endpoints in chapter B.7.3. The assessment relies mainly on the reviews of Bergqvist (1997), Moulder et al. (1999) and Elwood (2003). These reviews and the IEEE overview share the same deficiencies. The main lines of argumentation would be impossible in any other field of environmental health and closely resemble the strategy used to dismiss a power frequency exposure/childhood leukemia association. In the following paragraphs the assessment by IEEE will be briefly discussed.

> *Cluster studies, such as the one performed in Sutton Coldfield in the U.K. in response to a cluster of leukemia and lymphoma in adults living close to an RF broadcasting transmitter (Dolk et al. [R624]), are inherently difficult to interpret because of the impossibility of assessing all of the effects that chance variation might have contributed to the cluster. In the initial Sutton Coldfield study, the authors correctly concluded that no causal association could be drawn between the presence of the cluster and RF exposure from broadcasting towers (Dolk et al. [R625]) (Cooper et al. [R760]). (IEEE C 95.1 – 2005, p.75)*

First of all the Sutton Coldfield study was no cluster study but an ecological investigation. It is true that it was initiated by an unconfirmed report of a cluster of leukemia and lymphoma in the vicinity of a broadcasting transmitter but it proceeded independently of this initial report and used registry data on the population living within a radius of 10 km around the transmitter. The statement that such studies are “inherently difficult to interpret because of the impossibility of assessing all of the effects that chance variation might have contributed to the cluster" is ridiculous not only because the study is no cluster study but because it is impossible for any study to "assess all effects that chance variation might have contributed" to the endpoint under investigation. It is not mentioned that the study was supplemented by a larger investigation of another 20 high-power transmitters in Great Britain. The difficulties of interpreting ecological studies is related to the fact that potential confounders can only be related to a segment of the population but not to individuals and that in general duration and intensity of exposure are not known for individual members of the different strata. While evidence for an effect on brain tumor incidence from both studies (Dolk et al. 1997a, 1997b) is weak, there is consistent evidence for a relation to hematopoietic cancers. This evidence has been overlooked by the authors due their wrong assumption about the relation between proximity to the transmitter and exposure.

> *Inconsistent effects have been reported between residential proximity to other RF broadcast towers and adverse health endpoints (Bielski [R267]) (Maskarinec et al. [R579]) (Selvin and Merrill [R823]) (Michelozzi et al. [R858]) (Altpeter et al. [R977]) (Hallberg and Johansson [R995], [R996]) (Boscolo [R1012]), although many of these studies have significant flaws in their study design (making them difficult to interpret). (IEEE C 95.1 – 2005, p.75)*

Although it is not stated what these "inconsistent effects" might be, the statement is flawed in more than this respect. First of all the study by Bielski (1994) is an occupational investigation and not about residential proximity to RF broadcast towers, second three of these investigations (Selvin et al. 1992; Maskarinec et al. 1994; Michelozzi et al. 2002) included leukemia as an endpoint with indications of an increased incidence consistent with the studies from Great Britain (Dolk et al. 1997a, 1997b) and Australia (Hocking et al. 1996). Note that the study by Selvin et al. (1992), as stated previously, intended to compare different methods to assess the relationship between a point source and diseases and did erroneously assume a monotonous relationship between exposure and distance from a transmitter. Correcting this error there seems to be an increased probability of childhood leukemia in areas receiving the highest exposure from the Sutro tower. The other three investigations (Altpeter et al. 1995; Boscolo 2001; Hallberg & Johansson 2002) have nothing in common and hence cannot be inconsistent.

> *An increased incidence and mortality rate of childhood leukemia was reported in Australia with residential proximity to a specific RF broadcasting tower (Hocking et al. [R633]), although subsequent reanalysis of the data showed the results may have*

> *been influenced by other confounding variables within the study location (McKenzie et al. [R669]). (IEEE C 95.1 – 2005, p.75)*

This is another example how carelessly and sloppy the evidence is dealt with by the IEEE committee. The study of Hocking et al. (1996) was not about "proximity to a specific RF broadcasting tower" but about an area where three broadcasting towers are located. While there is always the possibility of confounders influencing results of an epidemiologic investigation, the 'reanalysis' of McKenzie et al. (1998) is seriously flawed and cannot support the cited statement. Hocking et al. (1996) combined the districts near the broadcasting area and those further away based on homogeneity analyses, while McKenzie et al. (1998) omitted one area with high incidence (and highest exposure) based on inspection of data. Any statistical analysis subsequent to such data picking is useless.

> *While scattered reports of adverse health effects associated with occupational exposure to RF do exist (Demers et al. [R36]) (Kurt and Milham [R68]) (Pearce [R110]) (Speers et al. [R125]) (Thomas et al. [R128]) (Pearce et al. [R199], [R211]) (Hayes et al. [R207]) (Cantor et al. [R268]) (Davis and Mostofi [R563]) (Tynes et al. [R570], [R605]) (Grayson [R592]) (Richter et al. [R747]) (Holly et al. [R838]) these studies are largely inconsistent with each other in terms of the adverse health endpoints affected, and often show no clear dose response with RF exposure. Many have serious flaws in their study design, contain limited or insufficient RF exposure assessment, and are generally inconsistent with the absence of findings of an association from other occupational studies (Tornqvist et al. [R131]) (Coleman [R142]) (Lilienfeld et al. [R146]) (Robinette and Silverman [R147], [R148]) (Siekierzynski et al. [R151], [R152]) (Wright et al. [R213]) (Coleman et al. [R214]) (Muhm [R506]) (Czerski et al. [R542]) (Hill [R568]) (Lagorio et al. [R616]) (Kaplan et al. [R647]) (Morgan et al. [R701]) (Gallagher et al. [R822]) (Groves et al. [R853]) (Wiklund [R1013]) (Armstrong et al. [R1014]). (IEEE C 95.1 – 2005, p.75)*

Even allowing for restrictions of space for a discussion of the evidence, greater nonsense has not been produced so far in this field as condensed in these two sentences. Putting higgledy-piggledy all sorts of studies together and then wondering about endpoints being inconsistent is an intellectual masterpiece. Of the occupational studies mentioned, three (Thomas et al. 1987; Speers et al. 1988; Grayson 1996) were about brain cancer, three about hematopoietic cancers (Pearce et al. 1985; Kurt & Milham 1988; Pearce 1988), two about testicular cancer (Hayes et al. 1990; Davis & Mostofi 1993), one about male (Demers et al. 1991) and two about female breast cancer (Cantor et al. 1995, Tynes et al. 1996) the latter including other cancers as well, and one about intraocular melanoma (Holly et al. 1996). Three further studies (Pearce et al. 1989; Tynes et al. 1992; Richter et al. 2000) investigated several or all malignancies. These studies differ not only in endpoints, study type (cohort, case-control, and cluster) but also in the methods of exposure assessment. Ignorance of the IEEE reviewers is underlined by the compilation of studies characterized by an "absence of findings of an association". Not only did several of these studies indeed indicate an association of cancer risk with EMF exposure (Lilienfeld et al. 1978; Robinette et al. 1980; Tornqvist et al. 1991; Armstrong et al. 1994; Lagorio et al. 1997; Groves et al. 2002) but two were no epidemiologic studies at all (Siekierzynski et al. 1974; Czerski et al. 1974) and several were rather addressing ELF exposure (Tornqvist et al. 1991; Wright et al. 1982; Coleman et al. 1983; Gallagher et al. 1991) and one (Wiklund 1981) was a cluster study in the telecommunication administration with uncertain type of exposure. Simply confronting studies finding an effect with others that were 'negative' is scientifically flawed and permits neither the conclusion that there is nor that there is no association between exposure and cancer risk. Even if all studies would have applied the same method, assessed the same endpoint and used the same exposure metric, studies reporting a significantly increased cancer risk are not outweighed by others that did not.

> *While micronuclei formation in workers occupationally exposed from broadcast antennas has been reported (Garaj-Vrhovac [R757]) (Lalic et al. [R791]), these findings were not verified in a larger study of more than 40 Australian linemen exposed under similar conditions (Garson et al. [R186]). (IEEE C 95.1 – 2005, pp.75-76)*

It goes without saying that also this statement is wrong. Garson et al. (1991) did not investigate micronuclei formation, their workers were considerably shorter exposed and it were not more than 40 linemen but 38 radio-lineman.

> *No clear association could be established between occupational exposures of parents to a number of agents, including RF, and effects (neuroblastoma) in their offspring (Spitz and Johnson [R289]) (De Roos et al. [R798]). (IEEE C 95.1 – 2005, p.76)*

What is meant by 'no clear association' is obscure. Spitz and Johnson (1985) found a significantly increased risk for paternal occupational exposure to electromagnetic fields, and also De Roos et al. (2001) found several jobs with paternal as well as maternal exposure to EMFs associated with an elevated risk for neuroblastoma in their children. However, broad groupings of occupations with ELF, RF EMF, as well as ionizing radiation (!) exposure did not reveal an increased risk.

> *One study reported a slight excess in brain tumors associated with combined exposure to RF and other exposures associated with electrical or electronic jobs, but not with RF alone (Thomas et al. [R128]). A study of a Polish military cohort reported a substantial excess of total cancer and several cancer sub-types with jobs associated*

> *with RF exposure (Szmigielski [R578]), (Szmigielski and Kubacki [R982]), although questions have been raised about severe bias in the exposure assessment of this study (Elwood [R665]) (Bergqvist [R1015]) (Stewart [R1133]). Studies by Milham of U.S. amateur radio operators reported an excess in one of nine types of leukemia assessed (see [R101], [R102], [R209], [R215], and [R569]), but not for total tumors, total leukemia, or brain tumors, and potential confounding factors might have included exposure to soldering fumes, degreasing agents and over-representation of a particular social class. (IEEE C 95.1 – 2005, p.76)*

Again the evidence is incorrectly summarized for all cited investigations. Thomas et al. (1987) found a significantly elevated risk for brain tumors among all men exposed to RF fields and in particular in those exposed for 20 or more years. There were indications that this elevated risk is due to a subgroup with electrical or electronics jobs. The group of those exposed in other jobs is heterogeneous and may contain subjects with low or no exposure (e.g. some groups of welders) and therefore lack of an association could be due to a dilution effect from exposure misclassification.

As mentioned previously criticism of the Polish military cohort study about exposure assessment is unfounded. Bergqvist (1997), Elwood (1999) and Stewart (2000) criticized that the military health board assessed a number of potential risk factors only for cancer cases. However, they overlooked that the study was a cohort and not a case-control study and that at no stage information about these factors entered the analysis and therefore couldn't affect the results in any way.

The study by Milham (1988a, 1988b) of radio amateur operators revealed a significantly increased standardized mortality ratio (SMR) for acute myeloid leukemia while the overall mortality and cancer mortality was significantly reduced relative to the country mortality rates. As mentioned previously this points to a 'healthy worker' effect as well as to an influence of life-style factors (mortality related to smoking and overweight were reduced). From the mentioned nine types of leukemia three with expectancies below one and no case observed couldn't be assessed, from the six remaining types five had elevated SMRs with AML, the most frequent type in adults, being significantly elevated.

The last portion of the IEEE review of epidemiology studies is dedicated to mobile phone investigations that are discussed in another contribution.

The following citation presents the IEEE summary in its full length:

> *The epidemiological evidence to date does not show clear or consistent evidence to indicate a causal role of RF exposures in connection with human cancer or other disease endpoints. Many of the relevant studies, however, are weak in terms of their design, their lack of detailed exposure assessment, and have potential biases in the data. While the available results do not indicate a strong causal association, they cannot establish the absence of a hazard. They do indicate that for commonly encountered RF exposures, any health effects, if they exist, must be small. Even though epidemiological evidence cannot rule out a causal relationship, the overall weight-of-evidence is consistent with the results of the long term animal studies showing no evidence of physiological, pathological or disease-specific effects. (IEEE C95.1 - 2005; pp.76-77)*

As already pointed out earlier (Kundi 2006) there is an intolerable tendency in the past years that confronted with an undeniable epidemiologic evidence of an association between an agent and adverse health effects such as cancer, interested parties take their resort to the concept of causality based on the wrong assumption evidence to "indicate a causal role" is a lot more difficult to provide. Unprecedented, however, is the notion of "a strong causal association". Whatever the meaning of this exceptional statement, the conclusion that, if health effects of commonly encountered RF exposures exist, they must be small, is wrong. To the contrary: considering the "lack of detailed exposure assessment" and other potential biases that predominantly lead to an underestimation of the risk, the evidence points to a quite substantial hazard. While the animal studies reviewed in another section of the IEEE standard document cannot be discussed here it should be underlined that they are generally insufficient to support either an increased risk or the lack of health relevant effects. Therefore they cannot be used in a weight-of-evidence statement as has been made by IEEE, that there is no evidence for adverse health effects of RF exposure.

VI. CONCLUSIONS

• Only few studies of long-term exposure to low levels of RF fields and brain tumors exist, all of which have methodological shortcomings including lack of quantitative exposure assessment. Given the crude exposure categories and the likelihood of a bias towards the null hypothesis of no association the body of evidence is consistent with a moderately elevated risk.

• Occupational studies indicate that long term exposure at workplaces may be associated with an elevated brain tumor risk.

• Although in some occupations and especially in military jobs current exposure guidelines may have sometimes been reached or exceeded, overall the evidence suggest that long-term exposure to levels generally lying below current guideline levels still carry the risk of increasing the incidence of brain tumors.

• Although the population attributable risk is low (likely below 4%), still more than 1,000 cases per year in the US can be attributed to RF exposure at workplaces alone. Due to the lack of conclusive studies of environmental RF exposure and brain tumors the potential of these exposures to increase the risk cannot be estimated.

• Epidemiological studies as reviewed in the IEEE C95.1 revision (2006) are deficient to the extent that the entire analysis is professionally unsupportable. IEEEs dismissal of epidemiological studies that link RF exposure to cancer endpoints should be disregarded, as well as any IEEE conclusions drawn from this flawed analysis of epidemiological studies.

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Table 1: Synopsis of epidemiologic studies of or including brain tumors (1987 – 2006)

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
Thomas et al. 1987	Northern New Jersey, Philadelphia, gulf coast of Lousiana/1979-1981/Case-control	Interviews with next-of-kin about occupational history – response rates: cases 74%, controls 63%; JEM (2 methods)	Death certificates verified through review of hospital records	age(m), (only males), year of death(m), area of residence(m), educational level, (lead, soldering fumes)	435/386	Cases: deaths of brain tumor or CNS tumors of white males (age>30) from death certificates Controls: deaths from other causes than brain tumors, epilepsy, etc.
Milham 1988	Washington, California/1979-1984/Cohort	Amateur radio operator license within 1/1979 to 6/1984	Mortality records	age, (only males), race, year of death	29	67829 operators, search of deaths in state registry through 1984
Selvin et al. 1992	San Francisco/1973-1988/Spatial cluster	Distance of center of census tract to microwave tower (Sutro tower)	SEER records	-	35	Search of cancer deaths of white individuals (age<21)
Tynes et al. 1992	Norway/1961-1985 /Occupational cohort	Job title in 1960 and 1970 censuses and expert categorization	Cancer registry	age, (only males)	119 overall, 6 in subgroup with possible RF exposure	Cohort of 37945 male workers identified that had jobs in 1960 with possible EMF exposure. among these 3017 with possible RF exposure
Grayson 1996	US Air Force/1970-1989/Nested case-control	Detailed job history and classification based on JEM (RF/MW exposure	Screening of hospital discharge records	age(m), race(m), military rank, (ELF and ionizing radiation	230/920	Cohort of ~880000 US Air Force members with at least one completed year of service within

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
		from frequent measurements)		exposure)		the study period, no follow up after subjects left service
Szmigielski 1996	Poland (military)/1971 - 1985/Occupational cohort	Allocation to RF/MW exposure group based on service records, documented measurements of military safety groups	Incident cases from central and regional military hospitals and military health departments	age, (only males)	~46	Annual number of ~127800 military career personnel, ~3720 RF/MW exposed per year
Hocking et al. 1996	Sydney (Australia)/ 1972-1990/Ecological	Municipalities within ~4 km of 3 TV broadcasting towers considered higher exposed as compared to 6 further away	Incident and death cases from cancer registry	age, sex, calendar period	740 (incident) 606 (mortality) 64 age<15 (incident) 30 age<15 (mortality)	Study population: inner area ~135000, outer area ~450000
Tynes et al. 1996	Norway/1961-1991/ Occupational cohort	Certified radio and telegraph operators 1920-1980 (98% worked on merchant ships); spot measurements on ships with old-	Cancer registry	age, (only females)	5	2619 women certified as radio or telegraph operators by Norwegian Telecom

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
		fashioned equipment				
Dolk et al. 1997a	Birmingham (GB)/ 1974-1986/Ecological	Living near a TV/FM radio transmitter (Sutton Coldfield)	Cancer registry	age, sex, calendar year, SES	332	Population (age≥15) ~408000 within 10 km of the transmitter
Dolk et al. 1997b	GB/1974-1986/ Ecological	Living near a high power (≥500 kW erp) transmitter (overall 21)	Cancer registry	age, sex, calendar year, SES	244	Population (age<15) within 10 km of one of 20 high power transmitters
Lagorio et al. 1997	Italy/1962-1992/ Occupational cohort	Working as RF heat-sealer operator	Cancer deaths from registry	age, (only females), calendar period, region	1	302 women employed 1962-1992 in a plastic-ware manufacturing plant as RF sealers
Finkelstein 1998	Ontario (Canada)/ 1964-1995/ Occupational cohort	Working as a police officer (possible handheld radar exposure)	Cancer registry	age, (only males), calendar year	16	20601 male officers of Ontario Police
Morgan et al. 2000	USA/1976-1996/ Occupational cohort	Jobs classified according to work with RF emitting devices with different output power	Death certificates from states' statistics offices	age, sex, period of hire	51	All U.S. Motorola employees with at least 1 day employment 1976-1996 (195775 workers, 2,7 million person-years)

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
Groves et al. 2002	USA/1950-1997/ Occupational cohort	6 occupational groups 3 with assumed low radar exposure (radar-, radio operator, aviation electrician's mate) and 3 with assumed high exposure (aviation electronics -, electronics -, fire control technician)	Death certificate from a state vital statistics office or National Death Index Plus	age at entry, (only males), attained age	88	40581 Navy Korean War veterans graduated 1950-54 from Navy technical schools; follow-up from graduation through 1997
Berg et al. 2006	Germany/2000-2003/ Case-control	JEM from occupational history collected in interview	Histological verified cases of glioma and meningioma	age(m), sex(m), region(m), SES, urban/rural, smoking, ionizing rad. exposure	Glioma 366/732 Meningioma 381/762	All histological confirmed cases of glioma and meningioma from 4 neurosurgical clinics (age: 30-69) (part.rate 84%); frequency matched controls from population registry (part.rate 63%)

SES…socio-economic status, JEM…job exposure matrix, erp…equivalent radiation power, RF/MW…radio frequency/microwaves, CNS…central nervous system, ELF…extremely low frequency

Table 2: Synopsis of main results of brain tumor studies (1987 – 2006)

Study	Endpoint	Exposure category	Meas.	Outcome [95% CI]
Thomas et al. 1987	Brain tumor deaths (ICD not specified)	Ever exposed to RF	OR	1.6 [1.0 – 2.4]
		Electrical/electronics job	OR	2.3 [1.3 – 4.2]
		Unexposed*		
		Ever exposed < 5 y	OR	1.0
		5-19 y	OR	2.3
		20+ y	OR	2.0
Milham 1988	Brain cancer deaths (ICD-8: 191)	All	SMR	1.39 [0.93 – 2.00]
		Novice[a]	SMR	0.34
		Technician	SMR	1.12
		General	SMR	1.75
		Advanced	SMR	1.74
		Extra	SMR	1.14
Selvin et al. 1992	Brain cancer deaths (ICD-O: 191.2)	> 3.5 km distance from tower*		
		≤ 3.5 km[b]	RR	1.16 [0.60 – 2.26]
Tynes et al. 1992	Incident brain cancer (ICD-7: 193)	All with possible EMF exposure	SIR	1.09 [0.90 – 1.41]
		Subgroup possible RF exposure[c]	SIR	0.49 [0.18 – 1.06]
Grayson 1996	Incident brain cancer (ICD-9: 191)	Never RF/MW exposed*		
		Ever exposed	OR	1.39 [1.01 – 1.90]
Szmigielski 1996	Incident nervous system & brain tumors	RF/MW exposed	OER	1.91 [1.08 – 3.47]
Hocking et al. 1996	Brain cancer (ICD-9: 191)	Outer area*		
		Inner area (incident, overall)	RR	0.89 [0.71 – 1.11]
		Inner area (mortality, overall)	RR	0.82 [0.63 – 1.07]
		Inner area (incident, age<15)	RR	1.10 [0.59 – 2.06]
		Inner area (mortality, age<15)	RR	0.73 [0.26 – 2.10]
Tynes et al. 1996	Incident brain cancer (ICD-7: 193)	All	SIR	1.0 [0.3 – 2.3]
Dolk et al. 1997a	Incident brain tumors (ICD-8/9: 191, 192)	0-2 km from transmitter	OER	1.29 [0.80 – 2.06]
		0-10 km from transmitter	OER	1.04 [0.94 – 1.16]
Dolk et al. 1997b	Incident brain tumors (ICD-8/9: 191, 192)	0-2 km from transmitter	OER	0.62 [0.17 – 1.59]
		0-10 km from transmitter	OER	1.06 [0.93 – 1.20]
Lagorio et al. 1997	Brain cancer deaths (ICD-9: 191)	RF sealer operator	OER	1 : 0.1
Finkelstein 1998	Incident brain cancer (ICD-9: 191)	All police officers	SIR	0.84 [0.48 – 1.36]
Morgan et al. 2000	Incident brain cancer (ICD-9: 191)	No RF exposure*		
		Low[d]	RR	0.92 [0.43 – 1.77]

Study	Endpoint	Exposure category	Meas.	Outcome [95% CI]
		Moderate	RR	1.18 [0.36 – 2.92]
		High	RR	1.07 [0.32 – 2.66]
Groves et al. 2002	Brain cancer deaths (ICD-9: 191)	Low radar exposure*		
		High radar exposure	RR	0.65 [0.43 – 1.01]
Berg et al. 2006	Incident glioma (ICD-O3: C71)	No occup. RF/MW exposure*		
		Probably no exposure	OR	0.84 [0.48 – 1.46]
		Probable exposure	OR	0.84 [0.46 – 1.56]
		High exposure	OR	1.22 [0.69 – 2.15]
		No high exposure*		
		High exposure <10 y	OR	1.11 [0.48 – 2.56]
		High exposure ≥ 10 y	OR	1.39 [0.67 – 2.88]
	Incident meningioma (ICD-O3: C70.0)	No occup. RF/MW exposure*		
		Probably no exposure	OR	1.11 [0.57 – 2.15]
		Probable exposure	OR	1.01 [0.52 – 1.93]
		High exposure	OR	1.34 [0.61 – 2.96]
		No high exposure*		
		High exposure <10 y	OR	1.15 [0.37 – 3.48]
		High exposure ≥ 10 y	OR	1.55 [0.52 – 4.62]

[a] From Milham 1988b, license classes as proxy for exposure duration
[b] Based on the assumption that exposure is higher near the microwave tower
[c] Computed based on Table 5 in Tynes et al. 1992
[d] Classification according to power output of equipment used for longest period of employment

OR…odds-ratio, SIR…standardized incidence ratio, SMR…standardized mortality ratio, RR…relative risk (rate ratio), OER…observed/expected ratio

SECTION 11

EVIDENCE FOR CHILDHOOD CANCERS (LEUKEMIA)

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July 2007

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I. Introduction

Since the seminal work of Wertheimer and Leeper (1979) more than two dozen epidemiological studies of childhood cancer and residential exposure to power-frequency EMFs were published, not counting some studies about electrical appliances and cluster observations. Although these studies make up an impressive body of evidence, there is an ongoing controversy whether the observed relationships between exposure to power-frequency EMFs and childhood cancer (in particular leukemia) can be causally interpreted. Based on these comparatively few empirical studies virtually hundreds of commentaries, reviews and meta-analyses have been produced, more often than not increasing confusion instead of clarifying the issue. In 2000 two pooled analyses of childhood leukemia, the endpoint most often studied, have been published, one (Ahlbom et al., 2000) that was restricted to 9 studies that fulfilled a number of inclusion criteria (a defined population base for case ascertainment and control selection and using measurements or historical magnetic field calculations for exposure assessment), and another (Greenland et al., 2000; Greenland 2003) including also wire-code studies. Both pooled analyses got essentially the same result: a monotonously increasing risk with increasing power-frequency (50Hz/60Hz) magnetic field levels. As a consequence, the International Agency for Research on Cancer (IARC) concluded in 2001 that power-frequency EMFs are a possible human carcinogen (Group 2B). This classification was based on the evidence from epidemiological studies of childhood leukemia because the panel rated the evidence from all other types of cancer, from long-term animal experiments and mechanistic studies as inadequate.

Typically, if an agent is classified as a Group 2B carcinogen, precautionary measures are taken at workplaces and special care is recommended if it is present in consumer products (e.g. glass wool, lead, styrene, Lindane, welding fumes). Concerning power-frequency EMFs the WHO International EMF Program made the following exceptional statement: “In spite of the large number data base, some uncertainty remains as to whether magnetic field exposure or some other factor(s) might have accounted for the increased leukaemia incidence.” (WHO Fact Sheet 263, 2001). This is the line of arguments that has been unswervingly followed by the electrical power industry since the early 1980’s. An endless chain of factors allegedly responsible for the ‘spurious’ positive association between power-frequency EMF exposure and cancer has been put forward, leading to nothing except waste of energy and money. In the last years, due to the fact that no confounding factor has been found that explains the increased leukemia risk, a slight change of arguments can be discerned that consists of pointing out the very low proportion of children (less than 1%) exposed to power frequency fields associated with a significantly increased risk. In fact, both pooled analyses concluded that there is little indication of an increased risk below 3 to 4 mG magnetic flux density.

In the following chapters we will present the epidemiological evidence, discuss potential biases and demonstrate that from a worst-case scenario the evidence compiled so far is consistent with the assumption of a much greater proportion of leukemia cases attributable to power frequency field exposure than previously assumed. The key problem identified is the lack of a bio-physical model of interaction between very weak ELF EMFs and the organism, tissues, cells, and biomolecules.

A. Epidemiological Studies of Power-Frequency EMF and Childhood Cancer

Table 11-2 gives a synopsis of studies on childhood cancer and exposure to power-frequency EMF, Table 11-3 presents the main findings of these investigations. Most often assessment of exposure was by measurements with 12 studies measuring for at least 24 hours up to 7 days, and 8 studies with spot measurements. Ten studies used distance from power lines as a proxy (some in combination with spot measurements) and 11 studies used wire codes classified according to the Wertheimer-Leeper or Kaune-Savitz methods. Several investigations covered more than one endpoint with hematopoietic cancers the most frequently included malignancies (overall 23 studies), followed by nervous system tumors (11 studies) and other cancers (8 studies). All childhood cancer cases were assessed by 8 investigations.

The most restrictive criteria for combining the evidence for an association between ELF magnetic fields (MF) exposure and childhood leukemia were applied by Ahlbom et al., (2000) that included 9 investigations. Table 11-1 shows the results of these investigations for the exposure category ≥ 4 mG (against < 1 mG as reference category). The studies included 3,203 children with leukemia, 44 of which were exposed to average flux densities of 4 mG or above. Thus only 1.4% of children with leukemia and less than 1% of all children in the studies were exposed that high in accordance with measurement samples from the general population in

Europe, Asia and America (Brix et al., 2001; Decat et al., 2005; Yang et al., 2004; Zaffanella, 1993; Zaffanella & Kalton, 1998).

Meta-analyses of wire-code studies (Greenland et al., 2000; Wartenberg, 2001) revealed similar results for childhood leukemia with estimates of risks around 2 for very high current codes but with considerable heterogeneity across studies.

Table 11-1: Results from nine studies included in Ahlbom et al. (2000) updated according to Schüz (2007) of residential MF exposure and risk of childhood leukemia

Country	Odds-Ratio*) (95%-CI)	Observed Cases
Canada	1.55 (0.65−3.68)	13
USA	3.44 (1.24−9.54)	17
UK	1.00 (0.30−3.37)	4
Norway	0 cases / 10 controls	0
Germany	3.53 (1.01−12.3)	7
Sweden	3.74 (1.23−11.4)	5
Finland	6.21 (0.68−56.9)	1
Denmark	2 cases / 0 controls	2
New Zealand	0 cases / 0 controls	0
Overall	2.08 (1.30 – 3.33)	49

*) 24-h geometric mean MF flux density of ≥ 4 mG against <1 mG

The only other endpoint except leukemia that has been investigated in several studies is nervous system tumors. The number of cases studied is too low to allow a differentiation according to diagnostic subgroups. Several papers have investigated childhood CNS tumors amongst other endpoints, including leukemia (Wertheimer & Leeper, 1979; Tomenius, 1986; Savitz et al., 1988; Feychting & Ahlbom, 1993; Olsen et al., 1993; Verkasalo et al., 1993; Tynes & Haldorsen, 1997; UKCCS, 1999; 2000), whereas others have solely investigated CNS tumors (Gurney et al., 1996; Preston-Martin et al., 1996; Schüz et al., 2001a). In most cases the time window was restricted to the postnatal period. Exposure was assessed based on residential proximity to overhead power lines, measurements and wiring configurations of houses. In a meta-analysis of childhood brain tumor studies (Wartenberg et al., 1998) estimates of risk were similar whether based on calculated fields (OR 1.4, 95% CI: 0.8 – 2.3), measured fields (OR 1.4, 95% CI: 0.8 – 2.4), wire codes (OR 1.2, 95% CI: 0.7 – 2.2), or proximity to electrical installations (OR 1.1, 95% CI: 0.7 – 1.7). The few studies published after this review do not change these figures substantially.

II. Discussion

Power frequency EMFs are among the most comprehensively studied risk factors for childhood leukemia. Except ionizing radiation no other environmental factor has been as firmly established to increase the risk of childhood leukemia, but for both there are ongoing controversies. Although data from atomic bomb survivors and radiotherapy of benign diseases (ringworm, ankylosing spondylitis, and thymus enlargement) clearly indicate a causal relationship between exposure and leukemia, for other conditions like living in the vicinity of nuclear power plants, diagnostic x-rays, exposure secondary to the Chernobyl incident evidence is less clear and therefore no agreement has been reached about these factors. Concerning power frequency EMFs few deny that the relationship is real and not due to chance, but still there is a controversy about the possibility that confounding, exposure misclassification, and selection bias is responsible for the observed relationship. Furthermore, it is often claimed that even if the exposure is causally related, due to the low attributable fraction no expensive measures to reduce exposure are warranted.

A. Confounding

A confounder is a factor that is associated with the agent in question as well as with the disease. Hence a confounder must be a risk factor for the disease. Concerning childhood leukemia it was clear from the very beginning that any suggested confounder must be purely speculative since there is no established environmental risk factor except ionizing radiation. Even if a condition can be found that is strongly associated with exposure to power frequency fields, if it is not associated with childhood leukemia it cannot confound the relationship. In the homogenous case, i.e. the association between EMF exposure and the confounder does not depend on disease status and the confounder - leukemia association is independent of exposure to power frequency EMFs, even a stronger assertion can be proven: power frequency EMF remains a risk factor if the risk associated with the confounder is smaller than that associated with power frequency EMFs. Equation (1) gives the bias-factor for the homogenous case and dichotomous exposure variables (that can, however, easily be extended to categorical or continuous exposure variables):

$$B_F = \frac{1+\pi_F(\Psi_{AF}\Psi_{DF}-1)}{[1+\pi_F(\Psi_{AF}-1)][1+\pi_F(\Psi_{DF}-1)]} \qquad (1)$$

(π_F is the prevalence of the confounder, Ψ_{DF} is the odds ratio for the confounder, and Ψ_{AF} is the odds ratio of the agent in question with respect to the confounder). From this equation it is immediately clear that if either Ψ_{DF} or Ψ_{AF} or both are 1 there is no bias. This equation can be used to obtain limiting conditions for the odds ratio of the confounder given specific associations with power frequency fields. This has been done by Langholz (2001).

Langholz (2001) investigated factors that have been proposed as possible confounders based on data from Bracken et al. (1998). None of these factors on their own explain the power frequency EMF - leukemia relationship. It has been criticized (Greenland, 2003) that too far reaching conclusions have been drawn based on the failure to discover a single factor that may explain the relationship, because combinations of such factors have not been addressed. However, even considering combinations of confounders it is unlikely that confounding alone explains the relationship between power frequency EMFs and childhood leukemia. Because of the rather small relative risks of around two for average exposure to $\geq$ 3 to 4 mG magnetic flux density or very high current codes there is, however, a possibility that bias due to a combination of confounding and other errors account for the increased risk. It will be shown in the last section that the most important aspect is the exposure metric. A much higher risk may be associated with exposure to power frequency fields. If this is actually the case the problem of bias of other provenience disappears.

Because the increased risk from high levels of exposure to power frequency EMFs is found in America, Europe, and Japan a confounder explaining this increased risk must not be quite strong and associated with magnetic fields of various sources but must also be present around the world. It is virtually impossible that such a risk factor has not yet been detected. Therefore, confounding alone as an explanation for the relationship with leukemia can practically be ruled out.

B. Exposure misclassification

Disregarding chance variations, non-differential exposure misclassification (i.e. misclassification that does not depend on disease status) always leads to an underestimation of the risk. The methods applied to calculate or measure MF in the residences of children are unlikely producing a bias that depends on the disease status. Hence, if exposure misclassification was present this will rather have reduced the overall risk estimate. Different effects must be considered whether sensitivity (the probability that a child that was exposed is correctly classified as exposed) or specificity (the probability that a child that was not exposed is correctly classified as not exposed) is affected by the assessment method. It can easily be shown that in the case of rare exposures the greater effect on the risk estimate is introduced by reduced specificity (hence by the presence of false positives). This may explain why longer measurement periods show a tendency to higher risk estimates. However, if the true exposure condition is actually not rare, sensitivity is more important and misclassification will result in a substantial underestimation of the true risk.

C. Selection bias

In studies that were relying on individual measurements selection bias may have played an important role. Participation rates were sometimes lower in controls and especially for families with lower SES. Schüz et al. (2001b) calculated in a simulation study that about two thirds of the increased risk could be due to selection bias. Although Wartenberg (2001) applying a meta-regression could not establish any aspect of study methodology that could account for the variation across studies, it is possible that the proportion of children exposed to high levels of MF has been underestimated in some studies.

D. Exposure metric

After measurements of MF over 24 hours or even longer periods were introduced lower risk estimates for measured fields as compared to estimates from wire codes were noted. This observation was termed the "wire code paradox". Although much of the discrepancies disappeared after the pooled analyses (Ahlbom et al., 2000; Greenland et al., 2000) were published, and also the comprehensive meta-analysis of Wartenberg (2001) could find no support for a systematic effect, still in some investigations there was indeed a stronger relationship to estimates from wire codes as compared to measurement. Bowman et al. (1999) and Thomas et al. (1999) published a comprehensive analysis of this aspect based on data of the Californian childhood leukemia study (London et al., 1991). They correctly noted the different error structure associated with measured fields and calculated fields from the wire codes that are more stable over time. They further pointed to the fact that the bias introduced by basing the risk estimate on exposure variables that are unbiased but prone to statistical variation will be towards the null. It can be shown that this bias is inversely related to the conditional variance of the exposure metric. Hence the higher the variance of the used exposure metric, conditional on the true one, the greater the bias of the risk estimate.

Up to now most considerations put forward were directed towards identification of factors and methodological issues that would explain a spurious relationship between power frequency EMFs and childhood leukemia. Hardly anyone asked the question: "Why is the risk estimated up to now so low?" This question should, however, been asked because there are a number of intriguing facts: First of all, in developing countries with low levels of electrification childhood leukemia incidence is manifold lower as compared to industrialized regions (Parkin et al., 1998). Although registry data in developing countries are less reliable and sparse the difference is too pronounced to be due to underreporting. The time trend of childhood leukemia in industrialized countries suggests that childhood leukemia in the age group below 4 to 5 years of age is essentially a new phenomenon that emerged in the 1920s. Milham and Ossiander (2001) suggest that the acute lymphoblastic leukemia peak is due to electrification. Given the evidence of the pooled analyses, risk increases as a function of average MF flux density reaching significance at the far end of the exposure distribution for children exposed to an average of 3 to 4 mG. This result is clearly not in line with the hypothesis that much if not all of childhood leukemia (at least for the most prevalent ALL type in the age group of 2 to 4 years) is due to power frequency EMFs. Obviously there are two conclusions possible: either the hypothesis is wrong or the data must be reinterpreted.

Another difficulty arises due to the fact that animal studies and in vitro tissue culture investigations provided equivocal evidence for a causal relationship between power frequency EMFs and cancer. There is a fundamental problem in clarifying the etiological role of the exposure in the development of leukemia. According to present theory (Greaves 1999; 2002; 2003; 2006; Wiemels et al., 1999) childhood leukemia is a consequence of several (at least two) genetic events one of which already occurred before birth. Factors affecting childhood leukemia may therefore be related to different critical exposure windows: the preconceptional, the prenatal, and the postnatal period. Preconceptional factors may affect the mother and the grandmother during pregnancy with the mother, as well as the father during spermatogenesis. During the prenatal period exposure of the mother during pregnancy and exposure of the fetus may differentially affect the first stage of the disease. In fact, there is convincing evidence that at birth around 1% of children show genetic deviations in cord blood cells (Wiemels et al., 1999; Eguchi-Ishimae et al., 2001; Mori et al., 2002) that could lead to leukemia conditional on them surviving and on additional events that lead to autonomous growth. Given this 100-fold higher incidence of early genetic events, a causal factor for childhood leukemia need not be directly genotoxic and not even mutagenic. A slight but continuous shift of the balance towards survival and proliferation of deviating clones will be sufficient to dramatically increase the incidence. Experimental investigations were generally insufficient to cover such effects.

Assuming that there is an exposure metric, intimately connected to average magnetic flux densities, and actually related to that condition responsible for the increased incidence of childhood leukemia, how does such a metric look like? Actually it is easy to derive the necessary conditions for such an exposure metric from bias considerations. There are only two such conditions that must be met:

a. The conditional expectancy $E(x|z) = z$ (or equal to a linear function of z); where x is the unknown exposure metric and z is the logarithm of the true average magnetic flux density the child is exposed to.

b. The conditional variance $V_{x|z}$ must be inversely related to z.

Based on the pooled analysis of Ahlbom et al. (2000) and assuming average magnetic flux density follows a log-normal distribution with mean 0.55 mG and a geometric standard deviation of 1, using the complete data set of cases and controls, the results of the pooled analysis can be reconstructed. However, *by varying the magnitude of the variance and the slope of the logistic function relating the purported exposure metric to the probability of developing childhood leukemia up to 80% of all cases can be attributed to the exposure.*

Fig.1 shows one of such Monte Carlo analyses. It can be seen that the bias of the risk estimate related to average MF flux density decreases as the level increases, however, the bias with respect to the assumed exposure metric reaches a factor of about 25 at levels above the third quartile.

While of course this analysis does not prove the assumption that most of childhood leukemia is due to electrification, it demonstrates that the data obtained so far do not contradict this assumption. It is of crucial importance to analyze existing measurement data for aspects of the exposure that are in line with conditions a. and b. stated above. These exposure conditions may be analyzed by in vitro studies to asses their potential the facilitate transformation of already genetically damaged cells.

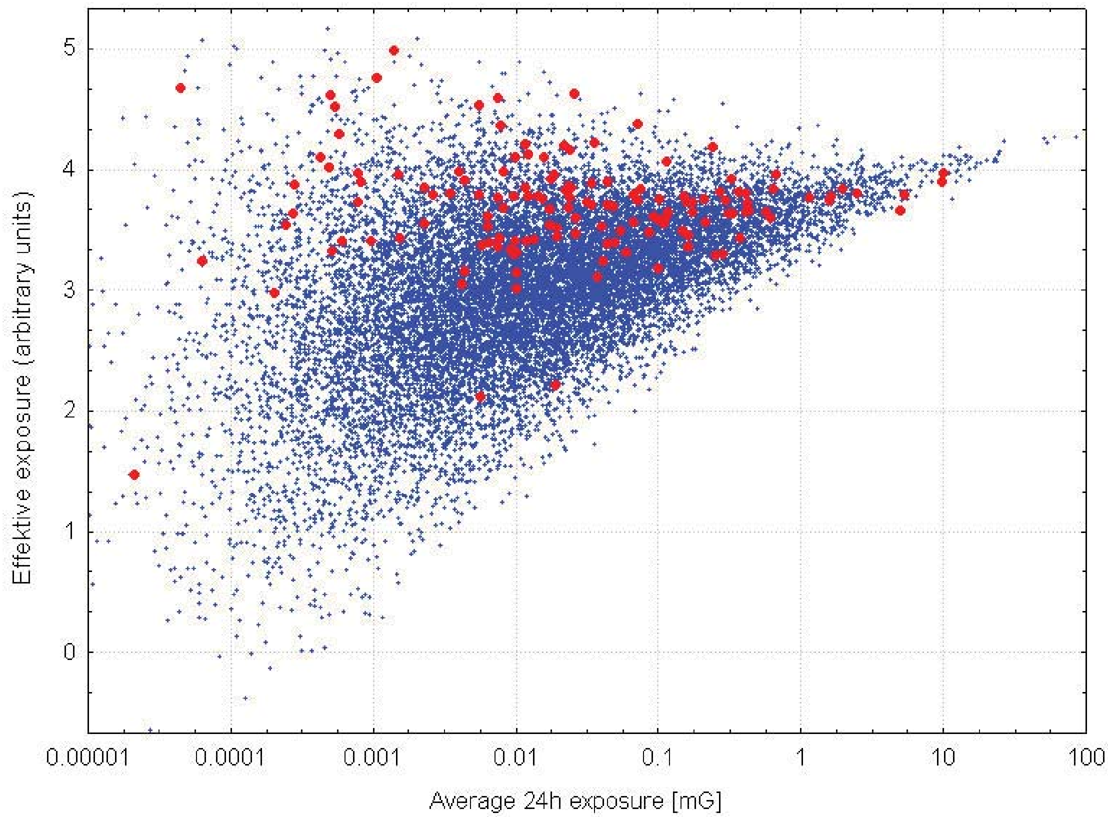

Fig. 1: Results of Monte Carlo simulation under the assumption of a log-normal distribution of average magnetic flux densities in the homes of children that are related to an assumed ‚effective' exposure metric that follows the conditions a. and b. mentioned in the text. Blue are controls and red children with leukemia. The purported ‚effective' exposure metric is associated with an attributable fraction of 80% and the odds-ratio for the highest quartile is around 50.

III. Conclusions

The only endpoint studied so far in sufficient detail is childhood leukemia. Brain and nervous system tumors were also studied in some detail but due to the diversity of these tumors no conclusions can be drawn.

Childhood leukemia is the most frequent childhood malignancy that peaks in the age group of 2 to about 5 years. This peak seems to have been newly evolved in the early quarter of the 20th century and may be due to electrification. This assumption is supported by the absence of this peak or it being much less pronounced in developing countries.

An overview of existing evidence from epidemiological studies indicates that there is a continuous increase of risk with increasing levels of average magnetic field exposure. Risk estimates reach statistical significance at levels of 3 to 4 mG. A low number of children are exposed at these or higher levels.

Considering the possibility that aspects of exposure to power frequency EMFs that have not yet been detected may account for a great proportion of cases there are two necessary steps to be taken: Concerted efforts must be undertaken to scrutinize existing data and collect new ones that should reveal whether or not exposure metrics exist that show the necessary conditions for an effective exposure metric; and, second, precautionary measures must be delineated that result in a reduction of all aspects of exposure to power frequency EMFs.

Exposure guidelines of IEEE and ICNIRP are solely derived from immediate effects such as nerve and muscle excitations. These guidelines are indeed sufficient to protect from such acute effects (although indirect effects from contact currents cannot be ruled out). Evidence for long-term chronic effects has been collected in the past decades and has reached a state that it cannot longer be denied that these effects are real. Only under very exceptional and remote conditions of a combination of several unknown confounders, selection bias and differential exposure misclassification the established relationship could be spurious. There is no other risk factor identified so far for which such unlikely conditions have been put forward to postpone or deny the necessity to take steps towards exposure reduction. As one step in the direction of precaution, measures should be implemented to guarantee that exposure due to transmission and distribution lines is below an average of about 1 mG.

- The balance of evidence suggests that childhood leukemia is associated with exposure to power frequency EMFs either during early life or pregnancy.

- Considering only average MF flux densities the population attributable risk is low to moderate, however, there is a possibility that other exposure metrics are much stronger related to childhood leukemia and may account for a substantial proportion of cases. The population attributable fraction ranges between 1-4% (Kheifets et al., 2007) 2-4% (Greenland & Kheifets 2006), and 3.3% (Greenland 2001) assuming only exposures above 3 to 4 mG are relevant. However, if not average MF flux density is the metric causally related to childhood leukemia the attributable fraction can be much higher. Up to 80% of childhood leukemia may be caused by exposure to power frequency EMF.

- Other childhood cancers except leukemia have not been studied in sufficient detail to allow conclusions about the existence and magnitude of the risk.

- IEEE guideline levels are designed to protect from short-term immediate effects, long-term effects such as cancer are evoked by levels several orders of magnitudes below current guideline levels.
- Precautionary measures are warranted that should reduce all aspects of exposure, because at present we have no clear understanding of the etiologically relevant aspect of the exposure.

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Table 11-2: Synopsis of childhood cancer epidemiologic studies (1979 – 2007)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Wertheimer & Leeper 1979	Greater Denver area, Colorado/ 1950-1973/ Case-Control	wire-codes by inspection (not blinded) of surroundings of residences occupied at birth and time of death	retrospective (1976-1977) assessment	all assessments within 22 days	age (m), sex, urbanization, SES, family pattern, traffic	344 cancer deaths (age<19) from files, matched controls from next entry in birth register or from alphabetical list
Fulton et al. 1980	Rhode Island/1964-1978/Case-Control	power lines (<45.72m from residences) assessed and MF calculated as combined weighted average (based on Wertheimer-Leeper measurements)	retrospective (1979) assessment	all assessments within same period	age(m), SES	119 leukemia patients (age<20) from Rhode Island hospital files; 240 control addresses from birth register
Tomenius 1986	Stockholm county/ 1958-1973/ Case-Control	inspection of visible electrical constructions within 150m of dwellings occupied at birth and diagnosis date; spot measurements at the door of the dwellings (blinded to case status)	retrospective (~1981) assessment	all assessments within same period	age(m), sex(m), district(m)	716 tumor cases (660 malignant, 56 benign) from cancer registry (age<19), matched controls from entry into birth register just before or after index case from same church district

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Savitz et al. 1988	Five-county Denver area, Colorado/1976-1983/Case-Control	wire-code of homes occupied prior to diagnosis (blinded to case status); spot measurements at the front door, in child's and parent's bedrooms and other rooms of frequent occupancy; interviews of mothers (in some cases fathers or adopted mothers)	retrospective (~1985) assessment	all assessments within same period	age±3y (m), sex(m), area(m), SES, traffic density, maternal age, maternal smoking	356 cancer cases (age<15) from cancer registry (71% interviewed, 36% measurements, 90% wire codes); 278 controls (79% resp.rate) from RDD (80% interviewed, 75% measurements, 93% wire codes)
Coleman et al. 1989	Four boroughs near London/1965-1980/ Case-Control	historical exposure by type and distance of electricity supply within 100 m of residences; distance to center of building assessed blinded to case status; calculations according to peak winter load of the power lines	retrospective assessment	all assessments within same period	age(m), sex(m), year of diagnosis(m)	84 leukemia cases (age<18) and 141 cancer controls from cancer registry

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Myers et al. 1990	Yorkshire/1970-1979/ Case-Control	assessment of overhead power lines within a distance depending on type of power line (100-500m) of home at birth; flux densities calculated from line load data and distance to center of dwelling	retrospective (1981-1989) assessment	all assessments within same period	age(m), sex(m), district(m), house type	374 cancer cases (age<15) from registries; 588 controls from nearest entry in birth register of the same district
London et al. 1991	Los Angeles County, CA/1980-1987/Case-Control	24-h MF measurements (IREQ/ EMDEX) at location of child's bed; EF, MF and static magnetic field spot measurements; Wertheimer-Leeper wire code (all facilities within 46m; blinded to case status); interviews with parents about use of appliances etc.	measurements 1987-1989	all assessments within same period	age±1 or 2 or 3y(m), sex(m), ethnicity(m), indoor pesticides, hair dryers, black&white TV, fathers occupational exposure to chemicals	232 leukemia cases (70% part.rate) from LA County Cancer Surveillance Program (age<11); 232 matched controls (90% part.rate) – 65 as friends of cases, others by RDD (5 digits cases, last 2 random)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Verkasalo et al. 1993	Finland/ 1970-1989/ Retrospective Cohort	estimated magnetic flux density from high-voltage power lines in the center of the building	cumulative and max. flux density any time between birth and diagnosis	n.a.	age, sex, calendar period	68300 boys and 66500 girls (age<20) identified having lived any time after birth in a house with a distance < 500m from a 110, 220, or 400 kV power line and an estimated flux density exceeding 0.1mG; 140 cancer cases from follow-up in cancer registry through 1990.
Feychting & Ahlbom 1993	Sweden/1960-1985/Nested Case-Control	calculations (blinded) based on historical load data, wire configuration and distance from 220 and 400kV power lines and spot measurements (several rooms, 5-min measurements, main current turned on and off)	the year closest to date of diagnosis	all assessments within same period	age(m), sex(m), parish(m), year of diagnosis, apartment/single house, traffic (NO_2)	142 cancer cases within the study base of children (age<16) living on a property <300m from any 220 or 400kV power line; 558 matched controls from the study base.

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Olsen et al. 1993	Denmark/1968-1986/ Case-Control	calculations based on estimated historical load of overhead transmission lines, transmission cables, and substations (50-400 kV)	retrospective up to 9 mo before birth	all assessments within same period	age(m), sex(m)	1707 cancer cases from registry (age<15) and 4788 matched controls from population register
Fajardo-Gutierrez et al. 1993	Mexico City/not specified/Case-Control	interview with parents including assessment of distance and type of transmission and distribution lines, power substations etc.	n.a.	n.a.	age±2y(m), SES	81 leukemia cases from two hospitals; 77 controls from orthopedics or traumatology department
Coghill et al. 1996	England/1986-1995/ Case-Control	E- and H-field probes designed for the study measured 24 h in the bedroom; data used only for the period 20:00 to 08:00	retrospective	parallel measurements in case and control homes	age(m), sex(m)	56 leukemia cases (age<15) from various sources (media advertising, self-help groups, Wessex Health Authority) and 56 controls (

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Gurney et al. 1996	Seattle area, Washington/1984-1990/Case-Control	wire-code by inspection of homes (blinded for case status) occupied within 3 y before diagnosis, electrical appliances by interview with mothers and mailed questionnaire	retrospective (1989-1994) assessment	all assessments within same period	age±2y(m), sex(m), area of residence(m), race, mothers education, family history of brain tumors, ETS, living on a farm, head/neck x-ray, head injury, epilepsy, fits	133 brain-tumor cases (age<20) (74% part.rate) by Cancer Surveillance System; 270 controls by RDD (79% part.rate)
Preston-Martin et al. 1996	Los Angeles County, California/1984-1991/ Case-Control	wire-code and outside spot measurements of homes occupied from conception to diagnosis (blinded for case status); 24h measurements in child's bedroom and another room for a subset; electrical appliances, occupation etc. by interviews with mothers	retrospective (1990-1992) assessment	all assessments within same period	age±1y(m), sex(m), year of diagnosis, SES, parents occupation, building type	298 brain tumor cases (age<20) (68% part.rate); 298 controls by RDD (70% part.rate)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Tynes & Haldorsen 1997	Norway/1965-1989/Nested Case-Control	Cohort (age <15) living in a ward crossed by a high-voltage power line (≥45kV in urban, ≥100kV in rural areas) in at least one of the years 1960, 1970, 1980, 1985, 1987, 1989.	Calculated historical fields	n.a.	age(m), sex(m), munici-pality(m), SES, type of building, number of dwellings	500 cancer cases (94%) from cancer registry; 2004 controls (95%) randomly selected from cohort
Michaelis et al. 1997a	Lower Saxony, Germany/1988-1993/ Case-Control	24h measurements (EMDEX II) in the child's bedroom and living room in dwellings where the child lived longest (not blinded to case status); perimeter measurements (measurement wheel) with recordings every foot (~30cm) when walking through the rooms and outside the house where the child lived for at least 1y.	measurements 1992-1995	all measurements within same period	age±1y(m), sex(m), SES, urbanization	129 leukemia cases (age<15) (59% part.rate) from register; 328 controls (167 from same district, 161 from random district) (53% part.rate) from government registration files

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Michaelis et al. 1997b	Berlin/1991-1994/ Case-Control (pooled with data from Michaelis et al. 1997a)	as above	not specified	not specified	age±1y(m), sex(m), SES, urbanization, age at diagnosis, West/East Germany	47 leukemia cases (age<15) (59% part.rate) from register; 86 controls (28% part.rate) from government registration files
Linet et al. 1997	Illinois, Indiana, Iowa, Michigan, Minnesota, New Jersey, Ohio, Pennsylvania, and Wisconsin/1989-1994/Case-Control	24h measurements (EMDEX C) in child's bedroom (blinded to case status); spot measurements in the residences and at the front door; wire coding of residences of residentially stable case-control pairs	~2 years	all measurements within same period	age(m), ethnicity(m), 8-digits phone number(m), sex, SES, time of measurem., urbanization, type of residence, birth order, birth weight, mother's age, medical x-ray	638 ALL cases (age<15) from register of Children's Cancer Group (78% part.rate); 620 controls from RDD (63% part.rate).

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Li et al. 1998	Taipei Metropol.Area (3 districts), Taiwan/ 1987-1992/ Ecological	high voltage transmission lines (69 -345kV) were mapped to 124 administrative regions; households with ≥50% intersecting a buffer zone of 100m around transmission lines	n.a.	n.a.	age (5y groups), calendar year	28 leukemia cases from registry in a study base of ~121.000 children (age<15); 7 cases within 21 cases outside a 100m corridor each side of a transmission line
Dockerty et al. 1998	New Zealand/1990-1993/Case-Control	24h measurements (Positron) in child's bedroom and another room (only for leukemia cases); interview with mothers	1-2 years	all measurements within same period	age(m), sex(m), SES, maternal smoking, living on a farm	303 cancer cases (age<15) from 3 registries (88% part.rate) – 121 leukemia cases; 303 controls from birth register (68% part.rate)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
UKCCS 1999	England, Scotland & Wales/1991(92)-1994(96)/Case-Control	spot measurements (EMDEX II) in child's bedroom, 90 min measurements in main family room, 48h measurements (20% of case-control pairs) at child's bedside; school measurements; weighted averages from info obtained by questionnaire; adjustments from historical load data	~2 years	<4 months in 98% of case-control pairs (spot), within 4 weeks (48h measurem.)	age (m), sex(m), district(m), deprivation index	2226 cancer cases (age<15) from registry (59% part.rate); 2226 matched controls from registry

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
McBride et al. 1999	Canada (5 provinces)/ 1990-1994(95)/Case-Control	48h personal measurements (Positron), 24h measurements in child's bedroom (75% cases, 86% controls); wire codes (78% cases, 85% controls) and residence perimeter and front door measurements (64% cases, 74% controls) (blinded to case status) (EMDEX C); interviews with parents	9 months average	2 months average	age±3-6mo (m), sex(m), area(m), maternal age, maternal education, income, ethnicity, number of residences	399 leukemia cases (age<15) (90% part.rate) from treatment centers and registry; 399 matched controls (76% part.rate) from health insurance/family allowance rolls
Green et al. 1999a	Greater Toronto Area, Canada/1985-1993/ Case-Control	48h personal measurements (Positron); spot measurements in child's bedroom and two other rooms; wire codes; interviews with parents	2-3 y average	~5 mo average	age±1y (m), sex(m), family income, siblingship, residential mobility, insecticides, mother's medication and exp. prior or during pregn.	201 leukemia cases (age<15) from hospital record (64% part.rate); 406 controls from telephone marketing list (10,000 residences) (63% part.rate)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Green et al. 1999b	Greater Toronto Area, Canada/1985-1993/ Case-Control	as above	2-3 y average	~5 mo average	as above	88 leukemia cases (age<15) from hospital record; 133 controls from telephone marketing list (10,000 residences)
Schüz et al. 2001a	West Germany/1993(90)-1997(94)/Case-Control	24h measurements (FW2a) under mattress of child's bed; 24h measurements (EMDEX II) in living room; perimeter measurements with recordings every foot (~30cm) when walking through the rooms			age(m), sex(m), community(m), SES, year of birth, urbanization, residential mobility, season, type of residence	514 leukemia cases (age<15) from cancer registry (61% of eligible) and 1301 controls from population registry (61% of eligible)
Schüz et al. 2001b	Lower Saxony/1988 – 1993 & Western Germany/1992-1994/ Case-Control	as above			age(m), sex(m), community(m), SES, urbanization	64 cases of CNS tumors (age<15) from registry and 414 controls from population registry

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Mizoue et al. 2004	Japan/1992-2001/Ecological	classification of 294 districts according to their proximity to high voltage power lines (66 and 220V); proportion of area of district (0%, <50%, >50%) within ±300m of a power line	n.a.	n.a.	age (5y groups)	14 cases (age<15) of hematopoietic malignancies identified from two hospitals (all that treated these malignancies)
Draper et al. 2005	England & Wales/ 1962-1995/Case-Control	computed distance from nearest overhead power line (132kV, 275kV, 400kV) of residence at birth	n.a.	n.a.	age±6mo(m), sex(m), district(m), SES	29081 cancer cases (age<15) identified from several registries (88% of total); 29081 controls from birth registers
Kabuto et al. 2006	Tokyo, Nagoya, Kyoto, Osaka and Kitakyushu metropolitan areas (Japan)/1999-2001/Case-control	7 days continuous MF measurement (EMDEX Lite) in child's bedroom; spot measurements in- and outside the house (EMDEX II)	~13 mo	~3 days	age±(≤)1y(m), sex(m), region(m), population size(m), father's and mother's education	321 ALL/AML cases (age<15) from several registries of childhood cancer study groups (49% part.rate); 634 controls from residential registry (29% part.rate)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Mejia-Arangure et al. 2007	Mexico-City/1995-2003/Case-Control	spot measurements (EMDEX II) at the front door; wire coding (blinded to case status)	not specified	not specified	age, sex, SES, birth weight, maternal age, traffic, district, family history of cancer	42 ALL/AML cases (age<16) with Down syndrome from 4 (all) treating hospitals; 124 healthy controls with Down syndrome from 2 centers

RDD…Random Digit Dialing, n.a…not applicable, MF…magnetic field, SES…socio-economic status, ALL…acute lymphoblastic leukemia, AML…acute myeloid leukemia

Table 11-3: Synopsis of main results of childhood cancer studies (1979 – 2007)

Study	Endpoint	Exposure category	Outcome [95% CI]
Wertheimer & Leeper 1979[a]	Leukemia	LCC* (birth address)	
		HCC	OR 2.28 [1.34 – 3.91]
	Lymphoma	LCC*	
		HCC	OR 2.48 [0.73 – 8.37]
	Nervous system tumors	LCC*	
		HCC	OR 2.36 [1.03 – 5.41]
	Others	LCC*	
		HCC	OR 2.38 [0.93 – 6.06]
	All hematopoietic	LCC*	
		HCC	OR 2.31 [1.41 – 3.77]
	All cancers	LCC*	
		HCC	OR 2.33 [1.59 – 3.42]
Fulton et al. 1980	Leukemia	Very low*[c]	
		Low	OR 1.1 [0.5 – 2.4]
		High	OR 1.2 [0.6 – 2.6]
		Very high	OR 1.0 [0.5 – 2.3]
Tomenius 1986	Leukemia	no 200 kV-line*	
		200 kV-line<150m	OR 1.09 [0.29 – 4.12]
	Lymphoma	no 200 kV-line*	
		200 kV-line<150m	OR 1.48 [0.35 – 6.35]
	Nervous system tumors	no 200 kV-line*	
		200 kV-line<150m	OR 3.96 [0.85 – 18.52]
	Others	no 200 kV-line*	
		200 kV-line<150m	OR 2.59 [0.70 – 9.66]
	All hematopoietic	no 200 kV-line*	
		200 kV-line<150m	OR 1.26 [0.47 – 3.34]
	All cancers	no 200 kV-line*	
		200 kV-line<150m	OR 2.15 [1.12 – 4.11]
	All cancers	<3mG birth dwelling*	
		≥3mG	OR 2.67 [1.18 – 6.08]

Study	Endpoint	Exposure category	Outcome [95% CI]
	All cancers	<3mG diagn. dwelling*	
		≥3mG	OR 2.60 [1.20 – 5.67]
Savitz et al.1988	Leukemia	<2mG low power use*	
		2+ mG	OR 1.93 [0.67 – 5.56]
	Lymphoma	<2mG low power use*	
		2+ mG	OR 2.17 [0.46 – 10.31]
	Brain tumors	<2mG low power use*	
		2+ mG	OR 1.04 [0.22 – 4.82]
	Others	<2mG low power use*	
		2+ mG	OR 0.96 [0.31 – 2.98]
	All hematopoietic	<2mG low power use*	
		2+ mG	OR 1.99 [0.57 – 5.14]
	All cancers	<2mG low power use*	
		2+ mG	OR 1.35 [0.63 – 2.90]
	Leukemia	<2mG high power use*	
		2+ mG	OR 1.41 [0.57 – 3.50]
	Lymphoma	<2mG high power use*	
		2+ mG	OR 1.81 [0.48 – 6.88]
	Brain tumors	<2mG high power use*	
		2+ mG	OR 0.82 [0.23 – 2.93]
	Others	<2mG high power use*	
		2+ mG	OR 0.75 [0.30 – 1.92]
	All hematopoietic	<2mG high power use*	
		2+ mG	OR 1.51 [0.68 – 3.35]
	All cancers	<2mG high power use*	
		2+ mG	OR 1.04 [0.56 – 1.95]
	All cancers	0-0.64 mG low power use*	
		0.65-0.99 mG	OR 1.28 [0.67 – 2.42]
		1.0-2.49 mG	OR 1.25 [0.68 – 2.28]
		2.5+ mG	OR 1.49 [0.62 – 3.60]

Study	Endpoint	Exposure category	Outcome [95% CI]
	All cancers	0-0.64 mG high power use*	
		0.65-0.99 mG	OR 1.13 [0.61 – 2.11]
		1.0-2.49 mG	OR 0.96 [0.56 – 1.65]
		2.5+ mG	OR 1.17 [0.54 – 2.57]
	Leukemia	LCC*	
		HCC	OR 1.41 [0.57 – 3.50]
	Lymphoma	LCC*	
		HCC	OR 1.81 [0.48 – 6.88]
	Brain tumors	LCC*	
		HCC	OR 0.82 [0.23 – 2.93]
	Others	LCC*	
		HCC	OR 0.75 [0.30 – 1.92]
	All hematopoietic	LCC*	
		HCC	OR 1.51 [0.68 – 3.35]
	All cancers	LCC*	
		HCC	OR 1.04 [0.56 – 1.95]
	All cancers	UG 2y before diagnosis*	
		VLCC	OR 0.96 [0.39 – 2.34]
		OLCC	OR 1.17 [0.65 – 2.08]
		OHCC	OR 1.40 [0.71 – 2.75]
		VHCC	OR 5.22 [1.18 – 23-09]
	All cancers	VLCC/OLCC*[b]	
		UG	OR 0.89 [0.51 – 1.55]
		OHCC	OR 1.25 [0.67 – 2.31]
		VHCC	OR 4.66 [0.95 – 22.76]
Coleman et al. 1989	Leukemia	≥100 m nearest substation*	
		50-99 m	OR 0.75 [0.40 – 1.38]
		25-49 m	OR 1.49 [0.61 – 3.64]
		0-24 m	OR 1.63 [0.32 – 8.38]

Study	Endpoint	Exposure category	Outcome [95% CI]
Myers et al. 1990	All cancers	<0.1mG*	
		0.1-0.3mG	OR 0.96 [0.37 – 2.51]
		≥0.3mG	OR 1.73 [0.59 – 5.07]
London et al. 1991	Leukemia	<0.68mG* (24h.measurem.)	
		0.68-1.18mG	OR 0.68 [0.39 – 1.17]
		1.19-2.67mG	OR 0.89 [0.46 – 1.71]
		≥2.68mG	OR 1.48 [0.66 – 3.29]
		<0.32mG (spot bedroom)*	
		0.32-0.67mG	OR 1.01 [0.61 – 1.69]
		0.68-1.24mG	OR 1.37 [0.65 – 2.91]
		≥1.25mG	OR 1.22 [0.52 – 2.82]
		UG/VLCC*	
		OLCC	OR 0.95 [0.53 – 1.69]
		OHCC	OR 1.44 [0.81 – 2.56]
		VHCC	OR 2.15 [1.08 – 4.26]
Verkasalo et al. 1993	Leukemia	≥4mG any time	SIR 1.55 [0.32 - 4.54]
	Lymphoma	≥4mG any time	SIR [0.00 - 4.19]
	Nervous system tumors	≥4mG any time	SIR 2.31 [0.75 - 5.40]
	Others	≥4mG any time	SIR 1.24 [0.26 - 3.62]
	All hematopoietic	≥4mG any time	SIR 1.49 [0.74 - 2.66]
	All cancers	≥4mG any time	SIR 1.66 [0.34 - 4.84]
Feychting & Ahlbom 1993	Leukemia	<1mG* (calculated)	
		1-2mG	OR 2.1 [0.6 – 6.1]
		≥2mG	OR 2.7 [1.0 – 6.3]
	Lymphoma	<1mG* (calculated)	
		1-2mG	OR 0.9 [0.0 – 5.2]
		≥2mG	OR 1.3 [0.2 – 5.1]

Study	Endpoint	Exposure category	Outcome [95% CI]
	Nervous system tumors	<1mG* (calculated)	
		1-2mG	OR 1.0 [0.2 – 3.8]
		≥2mG	OR 0.7 [0.1 – 2.7]
	Others	<1mG* (calculated)	
		1-2mG	OR 1.6 [0.6 – 4.3]
		≥2mG	OR 0.2 [0.0 – 1.7]
	All hematopoietic	<1mG* (calculated)	
		1-2mG	OR 1.7 [0.6 – 4.5]
		≥2mG	OR 2.2 [1.0 – 4.7]
	All cancers	<1mG* (calculated)	
		1-2mG	OR 1.5 [0.7 – 2.9]
		≥2mG	OR 1.1 [0.5 – 2.1]
Olsen et al. 1993	Leukemia	<1mG* (calculated)	
		1-4mG	OR 0.3 [0 – 2.0]
		≥4mG	OR 6.0 [0.8 – 44]
	Lymphoma	<1mG* (calculated)	
		1-4mG	OR 5.0 [0.7 – 36]
		≥4mG	OR 5.0 [0.3 – 82]
	CNS tumors	<1mG* (calculated)	
		1-4mG	OR 0.4 [0.1 – 2.8]
		≥4mG	OR 6.0 [0.7 – 44]
	All three combined	<1mG* (calculated)	
		1-4mG	OR 0.7 [0.2 – 2.0]
		≥4mG	OR 5.6 [1.6 – 19]
Fajardo-Gutierrez et al. 1993	Leukemia	Transformer station[d]	OR 1.56 [0.73 – 3.30]
		High voltage power line	OR 2.63 [1.26 – 5.36]
		Electric substation	OR 1.67 [0.65 – 4.35]
		Transmission line	OR 2.50 [0.97 – 6.67]

Study	Endpoint	Exposure category	Outcome [95% CI]
Preston-Martin et al.	Brain tumors	0.09-0.51 mG Md 24h *	
1996		0.52-1.02 mG	OR 1.5 [0.7 – 3.2]
		1.03-2.03 mG	OR 1.8 [0.7 – 4.5]
		2.04-10.4 mG	OR 1.2 [0.4 – 3.2]
		VLCC/OLCC*	
		UG	OR 1.9 [1.0 – 3.6]
		OHCC	OR 0.8 [0.6 – 1.2]
		VHCC	OR 1.2 [0.6 – 2.1]
Coghill et al. 1996	Leukemia	< 5 V/m E-field *	
		5-9 V/m	OR 1.49 [0.47 – 5.10]
		10-19 V/m	OR 2.40 [0.79 – 8.09]
		≥20 V/m	OR 4.69 [1.17 – 27.78]
Tynes & Haldorsen	Leukemia	<0.5mG (TWA birth-	
1997		diagn)*	OR 1.8 [0.7 – 4.2]
		0.5-1.4mG	OR 0.3 [0.0 – 2.1]
		≥1.4mG	
	Lymphoma	<0.5mG (TWA birth-	
		diagn)*	OR 1.0 [0.1 – 8.7]
		0.5-1.4mG	OR 2.5 [0.4 – 15.5]
		≥1.4mG	
	Nervous system tumors	<0.5mG (TWA birth-	
		diagn)*	OR 1.9 [0.8 – 4.6]
		0.5-1.4mG	OR 0.7 [0.2 – 2.1]
		≥1.4mG	
	Others	<0.5mG (TWA birth-	
		diagn)*	OR 2.9 [1.0 – 8.4]
		0.5-1.4mG	OR 1.9 [0.6 – 6.0]
		≥1.4mG	

Study	Endpoint	Exposure category	Outcome [95% CI]
	All hematopoietic	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 1.4 [0.7 – 3.1]
		≥1.4mG	OR 0.7 [0.2 – 2.4]
	All cancers	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 1.9 [1.2 – 3.3]
		≥1.4mG	OR 1.0 [0.5 – 1.8]
Michaelis et al. 1997a	Leukemia	<2mG (Median 24h)*	
		≥2mG	OR 3.2 [0.7 – 14.9]
		<2mG (Median night)*	
		≥2mG	OR 3.9 [0.9 – 16.9]
Michaelis et al. 1997b (pooled with previous)	Leukemia	<2mG (Median 24h)*	
		≥2mG	OR 2.3 [0.8 – 6.7]
		<2mG (Median night)*	
		≥2mG	OR 3.8 [1.2 – 11.9]
Linet et al. 1997	ALL	<0.65mG (TWA)*	
		0.65-1mG	OR 0.96 [0.65 – 1.40]
		1-2mG	OR 1.15 [0.79 – 1.65]
		2-3mG	OR 1.31 [0.68 – 2.51]
		3-4mG	OR 1.46 [0.61 – 3.50]
		4-5mG	OR 6.41 [1.30 – 31.7]
		≥5mG	OR 1.01 [0.26 – 3.99]

Childhood Cancer and EMF

Study	Endpoint	Exposure category	Outcome [95% CI]
Dockerty et al. 1998	Leukemia	<1mG (24h bedroom AM)*	
		1-2mG	OR 1.4 [0.3 – 7.6]
		≥2mG	OR 15.5 [1.1 – 224]
		<1mG (24h daytime room)*	
		1-2mG	OR 3.7 [0.7 – 18.8]
		≥2mG	OR 5.2 [0.9 – 30.8]
Li et al.1998	Leukemia	≥100m from transm.line	
		<100m	SIR 2.43 [0.98 – 5.01]
		Total population<15y	
		≥100m from transm.line	SIR 1.05 [0.64 – 1.58]
		<100m	SIR 2.69 [1.08 – 5.55]
UKCCS 1999	Leukemia	<1mG (estim.AM exp.)*	
		1-2mG	OR 0.78 [0.55 – 1.12]
		2-4mG	OR 0.78 [0.40 – 1.52]
		≥4mG	OR 1.68 [0.40 – 7.10]
	Central nervous system cancers	<1mG (estim.AM exp.)*	
		1-2mG	OR 2.44 [1.17 – 5.11]
		2-4mG	OR 0.70 [0.16 – 3.17]
		≥4mG	OR --
	Others	<1mG (estim.AM exp.)*	
		1-2mG	OR 0.81 [0.52 – 1.28]
		2-4mG	OR 1.08 [0.45 – 2.56]
		≥4mG	OR 0.71 [0.16 – 3.19]
	All cancers	<1mG (estim.AM exp.)*	
		1-2mG	OR 0.93 [0.72 – 1.19]
		2-4mG	OR 0.87 [0.53 – 1.42]
		≥4mG	OR 0.89 [0.34 – 2.32]

Study	Endpoint	Exposure category	Outcome [95% CI]
McBride et al. 1999	Leukemia	<0.8mG (lifetime	
		predicted)*	OR 0.74 [0.48 – 1.13]
		0.8-1.5mG	OR 1.15 [0.70 – 1.88]
		1.5-2.7mG	OR 1.02 [0.56 – 1.86]
		≥2.7mG	
		Low (Kaune-Savitz)*	
		Medium	OR 1.12 [0.77 – 1.64]
		High	OR 1.17 [0.74 – 1.86]
Green et al. 1999a	Leukemia	<0.4mG (spot measurem.)*	
		0.4-0.9mG	OR 0.47 [0.12 – 1.89]
		0.9-1.5mG	OR 0.75 [0.19 – 3.02]
		≥1.5mG	OR 1.47 [0.44 – 4.85]
Green et al. 1999b	Leukemia	<0.3mG (48h measurem.)*	
		0.3-0.7mG	OR 2.0 [0.6 – 6.8]
		0.7-1.4mG	OR 4.0 [1.1 – 14.4]
		≥1.4mG	OR 4.5 [1.3 – 15.9]
		<0.4mG (spot measurem.)*	
		0.4-0.8mG	OR 1.8 [0.5 – 6.1]
		0.8-1.6mG	OR 2.8 [0.8 – 10.4]
		≥1.6mG	OR 4.0 [1.2 – 13.6]
Schüz et al. 2001a	Leukemia	<1mG (Md 24h)*	
		1-2mG	OR 1.15 [0.73 – 1.81]
		2-4mG	OR 1.16 [0.43 – 3.11]
		≥4mG	OR 5.81 [0.78 – 43.2]

Study	Endpoint	Exposure category	Outcome [95% CI]
		<1mG (Md night-time)*	
		1-2mG	OR 1.42 [0.90 – 2.23]
		2-4mG	OR 2.53 [0.86 – 7.46]
		≥4mG	OR 5.53 [1.15 – 26.6]
Schüz et al. 2001b	CNS tumors	<2mG (Md 24h)*	
		≥2mG	OR 1.67 [0.32 – 8.84]
		<2mG (Md night-time)*	
		≥2 mG	OR 2.60 [0.45 – 14.9]
Mizoue et al. 2004	All hematopoietic	0% area intersection*	
		<50%	IRR 1.6 [0.5 – 5.1]
		>50%	IRR 2.2 [0.5 – 9.0]
Draper et al.2005	Leukemia	≥600m (from power line)*	
		200-600m	RR 1.22 [1.01 – 1.47]
		<200m	RR 1.68 [1.12 – 2.52]
	Brain tumors	≥600m (from power line)*	
		200-600m	RR 1.18 [0.95 – 1.48]
		<200m	RR 0.74 [0.47 – 1.15]
	Others	≥600m (from power line)*	
		200-600m	RR 0.96 [0.82 – 1.12]
		<200m	RR 0.88 [0.62 – 1.25]
Kabuto et al. 2006	ALL+AML	<1mG (1wk TWA)*	
		1-2mG	OR 0.93 [0.51 – 1.71]
		2-4mG	OR 1.08 [0.51 – 2.31]
		≥4mG	OR 2.77 [0.80 – 9.57]
	ALL+AML	<1mG (1wk night-time)*	
		1-2mG	OR 0.97 [0.52 – 1.79]
		2-4mG	OR 1.08 [0.47 – 2.47]
		≥4mG	OR 2.87 [0.84 – 9.88]

Study	Endpoint	Exposure category	Outcome [95% CI]
	ALL	<1mG (1wk TWA)*	
		1-2mG	OR 0.87 [0.45 – 1.69]
		2-4mG	OR 1.03 [0.43 – 2.50]
		≥4mG	OR 4.67 [1.15 – 19.0]
Gurney et al.2006	Brain tumors	UG*	
		VLCC	OR 1.25 [0.74 – 2.13]
		OLCC	OR 0.74 [0.34 – 1.61]
		OHCC	OR 1.07 [0.55 – 2.06]
		VHCC	OR 0.51 [0.16 – 1.60]
		LCC*	
		HCC	OR 0.86 [0.50 – 1.48]
Mejia-Arangure et al. 2007	ALL+AML	<1mG (spot)*	
		1-4mG	OR 0.94 [0.37 – 2.4]
		4-6mG	OR 0.88 [0.15 – 5.1]
		≥6mG	OR 3.7 [1.05 – 13]
		Low (Kaune-Savitz)*	
		Medium	OR 5.8 [0.92 – 37]
		High	OR 4.1 [0.66 – 25]

[*] Reference category
[a] Computed from table 5 of the original publication (could be biased due to not considering individual matching)
[b] Computed from table 5 of the original publication
[c] Quartiles of exposure distribution of controls (exposure calculated)
[d] Reference categories: Without the respective appliance near the residence
OR…odds-ratio, SIR…standardized incidence ratio, RR…relative risk, IRR…incidence rate ratio, LCC…low-current code, HCC…high-current code, UG…underground cable, VLCC…very low current code, OLCC…ordinary low current code, OHCC…ordinary high current code, VHCC…very high current code, Md…median, TWA…time weighted average, AM…arithmetic mean, ALL…acute lymphoblastic leukemia, AML…acute myeloid leukemia

SECTION 12

Magnetic Field Exposure:
Melatonin Production; Alzheimer's Disease; Breast Cancer

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Prepared for the BioInitiative Working Group
July 2007

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EXECUTIVE SUMMARY

Melatonin Production

Melatonin is a hormone produced primarily by the pineal gland, located in the center of the brain. Melatonin is evolutionarily conserved and is found in nearly all organisms. It has numerous properties which indicate that it helps prevent both Alzheimer's disease and breast cancer. There is strong evidence from epidemiologic studies that high (≥ 10 milligauss or mG)*, longterm exposure to extremely low frequency (ELF, ≤ 60 Hz) magnetic fields (MF) is associated with a decrease in melatonin production(Section II.)

Alzheimer's Disease

Amyloid beta (Aβ) protein is generally considered the primary neurotoxic agent causally associated with Alzheimer's disease (AD). Aβ is produced by both brain and peripheral cells and can pass through the blood brain barrier.

1. There is longitudinal epidemiologic evidence that high peripheral blood levels of Aβ is a risk factor for Alzheimer's disease (AD). (Section III.A.)
2. There is epidemiologic evidence that extremely low frequency (ELF, ≤ 60 Hz) magnetic fields (MF) exposure up-regulates peripheral blood levels of Aβ. (Section III.A.)
3. There is evidence that melatonin can inhibit the development of AD and, thus, low melatonin may increase the risk of AD (Section III.B.)
4. There is strong epidemiologic evidence that significant (i.e., high), occupational ELF MF exposure can lead to the down-regulation of melatonin production. The precise components of the magnetic fields causing this down-regulation are unknown. Other factors which may influence the relationship between MF exposure and melatonin production are unknown, but certain medications may play a role. (Section II.)
5. There is strong epidemiologic evidence that high occupational MF exposure is a risk factor for AD, based on case-control studies which used expert diagnoses and a restrictive classification of MF exposure. (Section III.C.)
6. There are no epidemiologic studies of AD and radiofrequency MF exposure and only one of non-acute radiofrequency MF exposure and melatonin, so conclusions are not yet appropriate. (Sections III.D and II.)

Breast Cancer

The only biological hypothesis which has been epidemiologically investigated to explain the relationship between MF exposure and breast cancer is that high* MF exposure can lower melatonin production, which in turn can lead to changes in the various biological systems which melatonin influences, including increased estrogen production and subsequent deleterious interactions with DNA, and decreased antiproliferative, antioxidant, DNA repair, and immune response capabilities. Thus lowered melatonin production can be expected to lead to increased risk of breast cancer.

1. *In vitro* and animal studies have demonstrated that (i) melatonin is a potent scavenger of oxygen and nitrogen radicals that cause DNA damage, (ii) melatonin interferes with estrogen's deleterious interactions with DNA, and (iii) melatonin inhibits the development of mammary tumors. (Section IV.A.)
2. Human studies indicate that MF exposure can decrease melatonin production. (Section II)
3. Human studies have found that low melatonin production is a likely risk factor for breast cancer. (Section IV.B.)
4. Human studies have shown that light-at-night and night shift work reduce melatonin production and are both risk factors for breast cancer. (Section IV.D.)
5. Occupational studies indicate that high MF exposure increases the risk of breast cancer. This is particularly true for a recent, large, and well-designed study from Poland (funded by the NCI, administered for the NCI by Westat, and conducted by Polish scientists).

   A recent, large, and well-designed, Swedish case-control study used a new ELF MF job exposure matrix, developed by the same group, which is nearly completely at odds with earlier exposure classifications. The female occupation generally thought to be the one with the highest ELF MF exposure (seamstress) was considered to have medium-low exposure, while several lower MF exposed occupations were considered high. The case-control study consequently found no risk associated with high MF occupations as rated by the new matrix, but did find that seamstresses had a statistically elevated risk of breast cancer. This job exposure matrix is likely inappropriate in many important instances and needs to be thoroughly reviewed. (Section IV.E.)
6. Studies of residential MF exposure and breast cancer have been generally negative. Measured residential MF exposure may not be related to actual individual exposure. Residential exposure is most often low, is usually not measured in residences that may be related to the latency period of breast cancer, does not take into consideration point sources of strong magnetic fields which may be related to real exposure, and thus often does not relate to actual exposure. Residential exposure studies are therefore not considered to be of importance for the purposes of this report. (Section IV.F.)
7. Quality radiofrequency studies are lacking. (Section IV.G.)

<u>Seamstresses</u>

As a group, seamstresses have proven to constitute an important occupation for the demonstration of a relationship between ELF MF exposure and both Alzheimer's disease and breast cancer. Seamstresses who use industrial sewing machines have very high and relatively constant MF exposure. This is because the motors of older AC machines are large and produce high levels of MFs, and are on and producing such fields even when no sewing is being done. The AC/DC transformers of DC industrial machines always produce a high field even when the machine is turned off (but not unplugged). In addition, rooms, in which a large number of such machines are used, even have relatively high ambient MF levels. Home sewing machines generally produce smaller MFs, but even these weaker MFs are substantial.

RECOMMENDATION Using the Precautionary Principal, mitigating exposure is a proper goal. Mean occupational exposures over 10 mG or intermittent exposures above 100 mG should be lowered to the extent possible. In situations where this is not feasible, the daily length of exposure should curtailed. Lowering MF exposure can be done by improved placement of the source(s) of magnetic fields (e.g., electric motors in sewing machines, AC/DC converters), shielding, and redesign. It is clear that re-engineering products can greatly lessen MF exposure, and possibly result in important innovations. It is noted that certain automotive models produce medium to high MFs, as do steel-belted radial tires (Milham *et al.*, 1999).

I. INTRODUCTION

All of the studies discussed have based exposure classifications using magnetic field (MF) measurements, not electric field (EF) measurements. We separately discuss extremely low frequency (ELF, ≤ 60 Hz) MFs and radiofrequency (RF) MFs. Furthermore, the discussion is primarily limited to investigations related to ELF MF exposure as a possible risk factor for Alzheimer's disease (AD), female breast cancer (BC), and the possible biological pathways linking ELF MF exposure to AD and BC incidence.

Exposure Concerns

Epidemiologic investigations are sensitive to errors in exposure assessment and errors in case-control designation. This is particularly true for MF exposure and for AD classification. With respect to occupational exposures, all job exposure matrices (JEM) are based on the measurement of a relatively small number of subjects in each job type. However, extensive measurements have been performed for workers in the electric utility industry and for seamstresses. Note, however, that the Swedish breast cancer study by Forssén *et al.* (2005) used only 5 essentially part-time seamstresses to determine exposure classification (Forssén *et al.* (2004).

The geometric mean MF exposure over the time period of observation is generally used for classification. For ordinal classifications, individual subjects in jobs with mean MF exposure measured close to a boundary value, e.g., between low and medium or between medium and high MF exposure, will frequently be incorrectly classified. This misclassification will generally lead to bias in the estimated risk towards 1, i.e., no risk.

For residential exposures, which do not include living near high power lines, measurements of necessity need to be taken at the current residence. Measurements are usually taken in several rooms at various locations, sometimes with and without electrical equipment turned on, but rarely (if ever) with water lines turned on. Thus, individualized exposures, e.g., sitting near a fuse box, being near one or more AC/DC transformers, use of specific brands and models of home sewing machines, being near a microwave oven in operation, and a myriad of other point sources are missed. Previous residences are usually not measured. Consequently, exposure classification is problematic for studies interested in risk associated with residential MF exposure.

* Unless otherwise specified, 'MF' or 'magnetic fields' refer to ELF MF fields. Also, unless otherwise specified, "high" MF exposure as used in this report means an exposure of at least 10 mG or (relatively frequenct) intermittent exposure above 100 mG, while "medium" exposure is an average exposure of between 2 and 10 mG or (relatively frequent) intermittent exposure above 10 mG. "Long-term exposure" means exposure over a period of years. Often, other researchers used a cut-point of around 2-3 mG, or sometimes even less, as a "high" average. The reviews of each study presented here detail the specific cut-point(s) used.

** Unless otherwise specified, 'MF' or 'magnetic fields' refer to ELF MF fields. Also, unless otherwise specified, "high" MF exposure as used in this report means an exposure of at least 10 mG, while exposure means exposure over a period of years. **

Diagnostic Concerns

AD is difficult to correctly diagnose. Non-specialists frequently incorrectly diagnose a patient as having AD. Exposure assessment and case-control classification errors bias the odds ratio (OR) estimator, when based on dichotomous exposure classification, towards the null hypothesis. When based on three (3) or more classification groups, exposure assessment and case-control classification errors in the types of analyses used most likely also lead to bias towards the null hypothesis.

> With respect to AD, unless the diagnosis is made by experts, there is a very large false positive rate. That is, community-based physicians often incorrectly diagnose dementia (versus depression, for example) and are particularly poor at determining the correct differential diagnosis of dementia. Most subjects with a diagnosis of dementia are simply assumed to have AD. This means that around 40% of all AD diagnoses by physicians who are not experts are incorrect. Diagnostic information on death certificates is even worse. Such a large error in caseness clearly biases the OR estimator towards the null hypothesis. (Many cases of AD go undiagnosed, especially early stage AD. However, this likely does not lead to a significant error rate in classification of controls.)
>
> With respect to breast cancer, the sub-type of breast cancer is generally recorded, e.g., estrogen receptor positive (ER+) or negative (ER-), which may very well be important with respect to MF exposure. However, sub-group analyses have not usually been performed.

Therefore, in reviewing published studies, particular emphasis is placed on these errors or caveats. Studies which assessed occupational exposures and those which assessed residential exposures are both discussed. Various algorithms for “MF exposure” have been used, and these will also be discussed. Not all studies, exposure data, and exposure algorithms are of equal value.

For both AD and BC, a possible biological pathway of particular importance is down- regulation of melatonin production as a result of longterm MF exposure. This is discussed in detail in this review.

A second possible biological pathway relates specifically to Alzheimer’s disease. Longterm MF exposure may increase the production of amyloid beta (Aβ), both in the brain and peripherally. Aβ, particularly the form with 42 amino acids ($A\beta_{1-42}$), is considered the primary neurotoxic compound causing AD. This pathway was proposed by Sobel and Davanipour (1996a). Two recent epidemiologic studies have provided some degree of confirmation. Thus, MF exposure may be a risk factor for AD through two complementary biological pathways. (See Sections III.A. and III.B.)

There may certainly be other potential biological pathways that will be identified. For example, melatonin interacts with certain cytokines which appear to affect immune responses. This may be relevant to the early elimination of cells which are either pre-malignant or malignant, thus preventing the development of overt breast or other cancers. However, the two pathways outlined above can most easily be evaluated in human studies, both population-based studies and clinical trials.

There are also several epidemiologic studies of melatonin production among workers with longterm occupational exposure to magnetic fields and a single study of women with high (vs low) residential MF exposure. These studies generally indicate that longterm MF exposure can lead to lowered melatonin production.

II. ELF Magnetic Field EXPOSURE and MELATONIN PRODUCTION

> <u>Conclusion</u>: *Eleven (11) of the 13 published epidemiologic residential and occupational studies are considered to provide (positive) evidence that high MF exposure can result in decreased melatonin production. The two negative studies had important deficiencies that may certainly have biased the results. There is sufficient evidence to conclude that longterm relatively high ELF MF exposure can result in a decrease in melatonin production. It has not been determined to what extent personal characteristics, e.g., medications, interact with ELF MF exposure in decreasing melatonin production.*

Eightly-five percent (85%) to 90% of pineal melatonin production is at night. Laboratory-based studies, using pure sinusoidal magnetic fields under experimental conditions have not found an effect on melatonin production (Graham *et al.*, 1996, 1997; *Brainard et al.*, 1999). However, several studies among subjects chronically exposed in occupational and residential environments have found an effect, while a few have not. The lack of an effect in laboratory settings may be because the MF exposure was too "clean" or because the duration of exposure was not sufficiently long, e.g., days, weeks, months.

The evidence indicates that high and MF exposures may lead to a decrease in melatonin production. Whether this decrease is reversible with a cessation of exposure is unknown. The extent of the decrease is hard to evaluate. It is also not yet possible to identify individual susceptibility to such a decrease in melatonin production.

Melatonin production is generally measured using its primary urinary metabolite, 6-sulphatoxymelatonin (aMT6s). Total overnight melatonin production is best estimated using complete overnight urine samples. Creatinine-adjusted aMT6s is slightly more correlated with cumulative melatonin estimates obtained from sequential overnight blood samples than is unadjusted aMT6s (Cook *et al.*, 2000; Graham *et al.*, 1998).

The human studies in occupational or residential environments which identified an effect are summarized below.

Positive Studies

- Assessment in the Finnish Garment Industry As a follow-up component to a Finnish study of MF exposures among garment factory workers, a small study of nighttime melatonin production was carried out (Juutilainen *et al.*, 1999). aMT6s excretion and creatinine were measured using complete overnight urine samples. Seamstresses (n=31), other garment workers (n=8), and non-exposed outside workers (n=21) participated. Observations were taken using complete overnight urine collections beginning on a Thursday night through the first morning void on Friday and on the subsequent Sunday night through the first morning void on Monday. There was very little variation between the two time period observations within each group, indicating that if there is an effect of MF exposure, it does not disappear over the weekend, at least among seamstresses using older industrial alternating current machines. The average Thursday-Friday non-adjusted aMT6s excretion level and the average aMT6s excretion level adjusted for creatinine were both statistically significantly lower ($p < 0.05$) among the workers in the garment factory compared to the controls, even after controlling for other factors associated with a lowering of melatonin levels: creatinine-adjusted aMT6s - 16.4 vs 27.4 ng/mg; unadjusted aMT6s - 5.1 vs 10.0 ng. There was no indication of a dose-response relationship among the garment factory workers.

  In a follow-up study, Juutilainen and Kumlin analyzed the same data in conjunction with a dichotomization of a measure of light-at-night (LAN), obtained from items in the original study questionnaire concerning use of a bedroom light at night, street lights outside the bedroom windows, and use of curtains which do or do not let light filter through. There was a significant interaction between the dichotomized MF exposure (high/low, i.e., cases vs controls) and LAN (yes/no). aMT6s was significantly lower for subjects with high MF with or without LAN. In addition, aMT6s was significantly lower among subjects with high MF and LAN exposure versus subjects with high MF and no LAN exposure. Alternatively, aMT6s was essentially identical for subjects with low MF exposure, regardless of the LAN status.

- Washington State Residential MF Exposure and Melatonin Study Women, aged 20 to 74, were selected for a study of the relationship of bedroom 60 Hz magnetic field levels and melatonin production (Kaune *et al.*, 1997a,b; Davis *et al.*, 2001a). Approximately 200 women were recruited based on magnetic field exposure information from a case-control study of breast cancer (PI: S Davis). About 100 women were sought whose bedrooms were at the high end of magnetic field level in the original study and about 100 were sought who were at the low end. Concurrent measurements of light at night in the bedrooms of these women were also obtained using a specially modified EMDEX II system. Mean magnetic field levels in the two groups differed by less than 1 mG. Thus, compared to MF exposures in many occupations, the women had quite low MF exposures. However, there was an inverse association between bedroom magnetic field levels and urinary aMT6s adjusted for creatinine levels on the same night, after adjusting for time of year, age, alcohol consumption, and use of medications. The association was strongest at those times of the year with the longest length of daylight and in women who were using medications that themselves were expected to attenuate melatonin production, e.g., beta and calcium channel blockers and psychotropic drugs.

- Crossover Trial of MF Exposure at Night and Melatonin Production Davis *et al.* (2006) conducted a randomized crossover trial among 115 pre-menopausal women with regular periods between 25 and 35 days apart, a body mass index between 18 and 30 kg/m^2, not using hormonal contraceptives or other hormones for at least 30 days before the study period, no history of breast cancer, no history of chemotherapy or tamoxifen therapy, not having been pregnant or breast-feeding within the previous year, not working any night shifts, not taking supplemental melatonin, phytoestrogens or isoflavones, and not eating more than 5 servings of soy-based foods within any one week. MF exposure or sham exposure was for 5 consecutive days. A random half of these women received MF exposure and then sham exposure one month later. The other random half had the exposures reversed. Ovulation was determined in the first, second and third months. The initial exposure (MF or sham) was in the second month during days 3-7 post-ovulation. The second exposure (sham or MF) was during the same days in the third month. The charging base of an electric toothbrush which produced a steady magnetic field was used. It was placed under the subject's bed at the head level so that the subject's head received 5-10 mG exposure above baseline. Complete overnight urine samples were collected on the night of the last exposure (MF or sham) in each of the two exposure periods. There were 2 subjects who did not ovulate during either exposure month and 13 who did not ovulate in one of the two months. Statistical adjustment was made for age, hours of darkness, body mass index, medication use, any alcohol consumption, and number of alcoholic beverages consumed. Because each subject was her own control, these adjustments probably did not affect the point estimates much. A regression analysis was undertaken. The 95% confidence interval (CI) of the regression slope was [-3.0 – +0.7] for all subjects and [-4.1 – -0.2] when the 15 subjects with "minor" protocol violations were eliminated from the analysis. These violations were (a) more than 40 days between the two assessments, (b) urine collections not on the same post-ovulation day, and (c) menstrual period started early. Only (b) appears to be really relevant because these subjects could have had less MF exposure. However, this information is not provided. Separate analyses were conducted for "medication users" (n=14) and non-users (n=101). The slope point estimate for the users was numerically smaller (-3.1) than for the non-users (-1.0). The authors state that the study "found that nocturnal exposure to 60-Hz magnetic fields 5 to 10 mG greater than ambient levels in the bedroom is associated with decreased urinary concentrations of (aMT6s)". It should be noted that the p-value of the slope estimate in the primary analysis (all participants) was greater than 0.05. However, the 95% CI, [-3.0 – +0.7], was quite unbalanced, with 0 being much closer to the upper end of the CI than the lower end. Also, the 95% CI, when the 15 subjects with minor protocol violations are eliminated is entirely below 0, and thus the point estimate is statistically significant at the 0.05 level. The authors also state the following: "(t)he more pronounced effect of magnetic field exposure on melatonin levels seen in medication users and in those with an anovulatory cycle suggest {sic} that individuals who have decreased melatonin levels already may be more susceptible to the effects of magnetic field exposure in further decreasing melatonin levels." The justification for this statement is not based on statistical testing.

- Residential High Power Lines, MF Exposure and aMT6s in the Quebec City Study Levallois *et al.* (2001) evaluated aMT6s among 221 women living near 735-kV power lines compared to 195 age matched women who live far away from such lines. The subjects wore magnetic field dosimeters for 36 consecutive hours to measure their actual MF exposure. The geometric mean 24-hour MF exposure was 3.3 mG among women living near a high power line and 1.3 mG among those who did not live near a high power line. Similarly, geometric mean exposure during sleep was 2.9 mG versus 0.8 mG for the two groups. No direct effect of MF exposure on creatinine-adjusted aMT6s was identified. However, living near a high power line and MF exposure interacted with age and body mass index (BMI; kg/m^2). Living near a high power line was associated with a significant decline in creatinine-adjusted aMT6s among older subjects and subjects with higher BMI. There were similar significant decreases related to age and BMI for women in the lowest quartile versus highest quartile. All analyses were adjusted for age, BMI, alcohol consumption in the previous 24 hours, medication use in the previous 24 hours, light at night, and education.

- Assessment in the Electric Utility Industry Burch *et al.* (1996, 1998, 1999, 2000, 2002) have reported on the association between levels of occupational daytime magnetic field exposure, non-work MF exposure, and the excretion of total overnight and daytime aMT6s among electric utility workers in several studies. These studies are among the largest to evaluate the relationships between MF exposure and melatonin production in humans, and are the only studies to use personal exposure monitoring of both MF and ambient light with a repeated measures design.

  - ✓ In their 1996 abstract, analyses were conducted for 35 of 142 electric utility workers enrolled in a larger study. MF exposure was assessed continuously at 15 second intervals for three 24-hour periods, with logs kept to identify work, sleep and other non-work time periods. Ambient light intensity was also individually measured. Complete overnight urine samples and post-work spot urine samples were collected at the same times over the 3 days. There were statistically significant inverse relationships between nocturnal aMT6s levels and log-transformed worktime mean MF exposure (p=0.013), geometric worktime mean MF exposure (p=0.024), and cumulative worktime MF exposure (p=0.008). There was no association, however, between sleep time and other time MF exposure levels and aMT6s levels during the daytime or nighttime, even though average cumulative MF levels were only somewhat higher during work: 18.3 mG-hours (work); 13.1 mG-hours (non-work); 12.6 mG-hours (sleep).

  - ✓ In their 1998 study, further results related to nocturnal aMT6s urinary excretion in relation to MF exposure were presented, using all 142 electric utility workers. The MF exposure metrics were geometric mean intensity, a rate-of-change metric (RCM), and the standardized rate-of-change metric (RCMS). RC was used as a measure of intermittence, while RCMS was used as a measure of the temporal stability of the serially recorded personal MF exposures. Statistical adjustments were made for age, month, and personal ambient light exposure. 24-hour mean MF exposure intensity, RCM, and RCMS were not associated with either nocturnal aMT6s or creatinine-adjusted aMT6s. However, there was an inverse relationship between residential RCMS and nocturnal aMT6s. The interaction between residential intensity and RCMS was inversely associated with total overnight urinary aMT6s excretion and with creatinine-adjusted nocturnal aMT6s excretion. There was a "modest" reduction in nocturnal aMT6s with more temporally stable MF exposures at work. The effect on nocturnal aMT6s was greatest when residential and workplace RCMS exposures were combined. The authors concluded that their study provides evidence that temporally stable MF exposure (i.e., lower RCMS) are associated with decreased nocturnal urinary aMT6s levels. Given the strong correlation between cumulative overnight serum melatonin levels and both total overnight urinary aMT6s and creatinine-adjusted aMT6s levels, these results indicate a reduction in overnight melatonin production.

- ✓ In their 1999 study, data from the same 142 electric utility workers were further analyzed. Personal exposure to workplace geometric mean and RCMS were evaluated for their effect on post-work urinary aMT6s measurements. No association between creatinine-adjusted aMT6s and the geometric mean MF exposure, before or after adjustment for age, calendar month and light exposure was found. However, MF temporal stability was associated with a statistically significant reduction in adjusted mean post-work aMT6s concentrations on the second ($p=0.02$) and third ($p=0.03$) days of observation. Light exposure modified the MF exposure effect. Overall, there was a significant ($p=0.02$) interaction between RCMS and ambient light exposure. Reductions in post-work aMT6s levels were associated with temporally stable MF exposures among workers in the lowest quartile of ambient light exposure (mostly office workers), whereas there was no RCMS effect among workers with intermediate or elevated ambient light exposure.

- ✓ In their 2000 study, Burch *et al.* examined aMT6s levels among a completely different population of 149 electrical workers, 60 in substations, 50 in 3-phase environments, and 39 in other jobs, using the same data collection strategy as was used in the previous study, but with the added characterization of specific work environments. The rationale for this study was based on previous observations in experimental animals suggesting that non-linear field polarization was critical in the reduction of melatonin production. These types of fields were expected to be present within substations and in the vicinity of 3-phase electrical conductors. Other conductors (1-phase, linear polarization) were selected as a control condition because they had not previously been associated with an alteration of melatonin production in laboratory animal studies. Thus, participating workers recorded the times they spent in these environments over the 3-day data collection period. Comparisons were made separately for subjects working in substation or 3-phase environments, or among those working in 1-phase environments. Adjusted mean aMT6s levels were compared statistically among workers in the lowest and highest tertiles of MF exposure, using either the geometric mean or the RCMS measurements. Among workers in either a substation or 3-phase environment for more than 2 hours, nocturnal aMT6s decreased 43% (p=0.03) when tertiles were based on geometric mean exposure and decreased 42% (p=0.01) when tertiles were based on RCMS. With RCMS tertiles, total overnight aMT6s excretion also decreased 42% (p=0.03) and post-work creatinine-adjusted aMT6s decreased 49% (p=0.02). With geometric mean tertiles, total overnight aMT6s excretion decreased 39% and post-work creatinine-adjusted aMT6s decrease 34%. However, neither of these decreases was statistically significant. No MF-related effects were observed among workers with less than 2 hours time spent in substation/3-phase environments. Similarly, no reduction in aMT6s levels were observed among workers in 1-phase environments.

✓ In 2002, Burch *et al.* studied two consecutive cohorts of electric utility workers using the same data collection strategy to evaluate the effects of cellular telephone use and personal 60 Hz MF exposure on aMT6s excretion. The sample sizes were 149 for Cohort 1 (from the 2000 study) and 77 for Cohort 2. Total overnight and post-work urine samples and self-reported workplace cell phone use were obtained over three (3) consecutive workdays. ELF MF and ambient light exposure were also measured with specially adapted personal dosimeters. The outcome of interest was melatonin production as measured by aMT6s. The cut-point for high versus low cell phone use was 25 minutes per day. Only 5 worker-days of cell phone use more then 25 minutes were reported in Cohort 1 versus 13 worker-days in Cohort 2. No differences in aMT6s production were found in Cohort 1. However, for Cohort 2 there were significant linear trends of decreasing overnight aMT6s and creatinine-adjusted aMT6s levels with increasing cell phone use. There was also a marginally significant increasing trend in post-work creatinine-adjusted aMT6s with increasing cell phone use. Finally, there was a combined effect of cell phone use and ELF MF exposure on aMT6s excretion: among workers in the highest tertile of ELF MF exposure, those who used a cell phone for more than 10 minutes had the lowest overnight aMT6s and creatinine-adjusted aMT6s levels compared to those with lower ELF MF exposure or cell phone use. All analyses used a repeated measures method and were adjusted for age, month of participation, and light exposure.

- Swiss Railway Worker Study Pfluger and Minder (1996) studied 66 railway engineers operating 16.7 Hz electric powered locomotives and 42 "controls". Mean MF exposure at the thorax for the engineers was above 150 mG and approximately 10 mG for the controls. Thus most controls also had high MF exposure, certainly compared to residential and most occupational MF exposures. Morning and early evening (post-work) urine samples were used to measure aMT6s. Evening aMT6s values were significantly lower following work periods (early, normal or late shifts) compared to leisure periods for the engineers, but not for the controls. Also, morning samples did not differ between leisure and work mornings. This indicates that there was at least somewhat of a recovery from the worktime MF exposures. Evening aMT6s values did not differ between work time and leisure time for either engineers or controls. However, there was a rebound in morning aMT6s between a work period and leisure period. Pfluger and Minder did not report the results of a comparison of nighttime aMT6s levels between engineers and controls.

- Video Display Unit Studies Non-panel video display screens, e.g., computer monitors, produce significant MF exposure despite improvements over the last decade or so. Arnetz and Berg (1996) studied 47 Swedish office workers who used video display units (VDU) in their work in the 1980s. Circulating melatonin levels significantly decreased during work, but not during a day of "leisure" in the same environment. Nighttime melatonin production was not observed. In 2003, Santini *et al.* conducted a similar, but quite small, study of 13 young female office workers, 6 of whom worked for at least 4 hours per day in front of a video screen. Overnight urine samples were used to measure aMT6s. The aMT6s values of the exposed workers was 54% lower ($p<0.01$) compared to the non-exposed workers.

Negative Studies

- Italian Study of Workers Gobba *et al.* (2006) recruited 59 workers, 55.9% of whom were women, for a study of melatonin production and MF exposure. Actually more workers were recruited, but urine samples for only those subjects who did not get up to urinate during sleep time were assayed. Creatinine-adjusted aMT6s was measured using a Friday morning urine sample and the following Monday morning urine sample. Mean age was 44.4 years (standard deviation, 9.2). Exposure during worktime was measured over a three-day period. The logarithm of the time weighted average (TWA) and the percent of time above 2 mG were used as the measures of exposure. 2 mG was the cut-point between low and high exposure. 52.5% were in the low exposed group; a larger percentage of men than women were in the low exposed group. Occupations included clothing production (n=26), utility companies (14), teachers (6), engineering industry (5), and miscellaneous (8). There were no significant differences in creatinine-adjusted aMT6s values based on the logarithm of the TWA or percent of observations above 2 mG.

- Occupational MF Exposures among 30 Males Subjects in France Touitou *et al.* (2003) studied 15 men exposed to occupational magnetic fields for between 1 and 20 years and age-matched15 controls. All subjects were free of acute or chronic diseases, had regular sleep habits, did not do night work, took no transmeridian airplane flights during the preceding 2 months, took no drugs, were nonsmokers, and used alcohol and coffee in moderate amounts. Furthermore, they did not use electric razors or hair dryers during the study or in the 24 hours prior to blood sampling. All of the 15 MF exposed men worked in high voltage electrical substations. They also lived near substations. None of the controls had an occupation associated with MF exposure. Exposed subjects had a mean exposure of 6.4 mG during work and 8.2 mG during other times. For the control subjects, the mean exposure was 0.04 mG, both during the day and at other times. Blood samples were taken hourly from 8:00 pm until 8:00 am in a standard manner. All urine between these times was collected. Melatonin concentration (pg/ml) was measured in each blood sample. The study was done in the autumn. The 12 hour melatonin blood concentration curves for the exposed and non-exposed subjects are almost identical. The creatinine-adjusted aMT6s levels are also nearly identical. No analyses were conducted based on length of time in the occupation.

III. ALZHEIMER'S DISEASE

A. Alzheimer's Disease Specific Pathway: Over-Production of Peripheral Amyloid Beta Caused by MF Exposure

<u>Conclusion</u>: *There is now evidence that (i) high levels of peripheral amyloid beta are a risk factor for AD and (ii) medium to high MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high MF exposure to brain cells likely also increases these cells' production of amyloid beta.*

Sobel and Davanipour (1996a) have published a biologically plausible hypothesis relating MF exposure to AD, based on the unrelated work of many researchers in several different fields. The hypothesized process involves increased peripheral or brain production of amyloid beta (Aβ) as a result of MF exposure, and subsequent transportation of peripheral Aβ across the blood brain barrier. Figure 1 provides a schematic outline of the hypothesis. Each step in the proposed pathway is supported by *in vitro* studies.

Two versions of the amyloid beta protein have been identified. They are identical, except one is longer, 42 versus 40 amino acids. These are specified, respectively, by $A\beta_{1-42}$ and $A\beta_{1-40}$. $A\beta_{1-42}$ is considered the more neurotoxic of the two.

This hypothesis has not yet been fully tested. However, two recent studies of elderly subjects and electrical workers, respectively, have provided important initial support. The Mayeux *et al*. (1999, 2003) papers demonstrate that higher levels peripheral $A\beta_{1-42}$ are a risk factor for AD. The Noonal et al. (2002a) paper demonstrates that MF exposure can increase the peripheral levels of $A\beta_{1-42}$ and that contemporaneous blood levels of melatonin are inversely associated with peripheral levels of $A\beta_{1-42}$.

- Mayeux *et al.* (1999, 2003) conducted a population-based, longitudinal study of elderly subjects who were cognitively normal at baseline and found that higher peripheral blood levels of $A\beta_{1-42}$ were prognostic of subsequent development of AD. The 2003 paper had a longer follow-up period and 282 additional subjects (169 vs 451).

  In the first paper, 105 subjects, cognitively normal at baseline, were followed for an average of 3.6 years. The mean age at baseline was 74.3 +/- 5.3 years. Sixty-four (64) subjects developed AD. Table 1 provides the baseline and follow-up means for age, education, $A\beta_{1-42}$, $A\beta_{1-40}$, and the ratio $A\beta_{1-42}/A\beta_{1-40}$. The subjects who developed AD were older at baseline, had nearly two years less education, and higher $A\beta_{1-42}$, $A\beta_{1-40}$, and $A\beta_{1-42}/A\beta_{1-40}$. All mean differences were significant at the p=0.001 level, except for the ratio, which was significant at the p=0.05 level.

For $A\beta_{1-42}$, the OR for AD, based on the actual $A\beta_{1-42}$ values, was 1.0114, p = 0.006. Thus, for example, the OR for an individual with an $A\beta_{1-42}$ value 10 pg/ml above the cutpoint for the 1st quartile (24.6 pg/ml) is estimated to be $(1.0114)^{10} = 1.12$, an increase of 12%; for an individual with an $A\beta_{1-42}$ value 40 points above this cutpoint, the estimated increase in risk is 57%. A similar analysis for $A\beta_{1-40}$ did not yield a significant result.

Subjects were then divided into quartiles based on their $A\beta_{1-42}$ values. For $A\beta_{1-42}$ there was a highly significant (p=0.004) trend across quartiles. The adjusted odds ratios (OR) for the 2nd – 4th quartiles were 2.9, 3.6, and 4.0, using logistic regression. The latter two were statistically significant at the 0.05 level. The ranges for the 3rd and 4th quartiles were 45.9 – 85.0 pg/ml and > 85.0 pg/ml, respectively. For the 2nd quartile, the significance level of the OR was not provided; however, the 95% confidence interval (CI) was [0.9 – 6.8]. Perhaps because the per unit analysis was not significant for $A\beta_{1-40}$, an analysis using quartiles was not reported.

In the second paper (Mayeux *et al*., 2003), follow-up of patients was up to 10 years and there were 451 patients who were cognitively normal at baseline, versus 169 in the initial paper. Table 2 contains the same information for this study as is provided in Table 1 for the initial study. Eighty-six (86) of the 451 subjects developed AD. Presumably, the additional subjects had had their peripheral amyloid beta assayed after the submission of the original paper. Again, the $A\beta_{1-42}$ values were divided into quartiles, based on the 451 subjects who were cognitively normal at their last follow-up. The adjusted relative risk (RR) estimates for the 2nd – 4th quartiles were 1.3, 1.9, and 2.4, using Cox survival analysis. The latter two were statistically significant at the 0.05 and 0.006 levels, respectively. The ranges for the 3rd and 4th quartiles were 60.2 – 84.15 pg/ml and ≥ 84.15 pg/ml, respectively. For the 2nd quartile, the significance level of the OR was again not provided; however, the 95% confidence interval (CI) was [0.6 – 2.1].

> The mean levels of $A\beta_{1-40}$, $A\beta_{1-42}$, and $A\beta_{1-42}$/ $A\beta_{1-40}$ at baseline in the second paper were 133.9 pg/ml, 62.2 pg/ml, and 0.50. In the initial paper, the comparable figures were 120.5 pg/ml, 63.2 pg/ml, and 0.57. The means for $A\beta_{1-42}$ and $A\beta_{1-42}$/ $A\beta_{1-40}$ are quite similar in the two studies. However, the means for $A\beta_{1-40}$ are quite different, so there were most likely several subjects who were not in the initial report, and who had $A\beta_{1-40}$ assays which were very high. These subjects were evidently almost all in the cognitively normal group. This is because in the AD groups, the $A\beta_{1-40}$ means were 134.7 and 136.2 pg/ml. However, in the cognitively normal group, the means were 111.8 and 133.3 pg/ml. Thus, the additional 260 subjects with did not develop AD (365-105=260) had an average $A\beta_{1-40}$ of 142.0 pg/ml. Such a large difference is left unexplained in the Mayeux *et al*. (2003) paper.

Mayeux *et al*. (1999) comment that “cerebral deposition of $A\beta_{1-42}$ is unlikely to result directly from increased plasma $A\beta_{1-42}$”. However, studies by Zlokovic and colleagues provide a basis for concluding that, in fact, peripheral $A\beta_{1-42}$ is likely to cross the blood brain barrier, perhaps chaperoned by apolipoprotein E (ApoE), particularly the ε4 isoform (see Sobel & Davanipour, 1996a). Currently, the relative amounts of peripheral and cerebral $A\beta_{1-42}$ or $A\beta_{1-40}$ which aggregate are unknown.

> Two newly developed PET scan techniques, however, provide the ability to investigate the relative amounts in humans (Klunk *et al.*, 2004; Ziolko *et al.*, 2006; Small *et al.*, 2006) . It is also straightforward to use labeled amyloid beta to determine the rate at which peripheral amyloid beta is transported to the brain, at least in animal models and perhaps also in humans.

- Noonan *et al.* (2002a) examined 60 electric utility workers in studying the relationship between measured MF exposure during the work day and serum Aβ_{1-42} and Aβ_{1-40} (square root transformed) levels. MF exposure was individually determined by wearing a dosimeter at the waist during work time. Blood samples were obtained between 2:50 pm and 4:50 pm. The primary findings were as follows:
    - **i.** there was an inverse association between physical work and Aβ levels;
    - **ii.** there was an apparent trend for the Aβ_{1-42}, Aβ_{1-40}, and Aβ_{1-42}/ Aβ_{1-40} levels to be higher for higher magnetic field exposure (significance not provided); and
    - **iii.** the differences (Table 3) in Aβ levels between the highest (≥ 2 milliGauss (mG), n=7) and lowest (< 0.5 mG, n=20) exposure categories were 156 vs 125 pg/ml (p=0.10) for Aβ_{1-40}, 262 vs 136 pg/m (p=0.14) for Aβ_{1-42}, and 1.46 vs 1.03 for Aβ_{1-42}/ Aβ_{1-40} (significance not provided).

  There was a 93% increase in Aβ_{1-42}, a 25% increase in Aβ_{1-40}, and a 42% increase in the ratio Aβ_{1-42}/ Aβ_{1-40} between the lowest and highest MF exposure categories. The 2 mG cutpoint for the highest category is the cutpoint generally used for medium (or at times high) MF exposure in epidemiologic studies. Thus, while the sample size was small, this study provides some evidence that MF exposure may result in higher peripheral production of Aβ for exposures above 2mG.

  Melatonin production was estimated using urinary 6-sulphatoxymelatonin (aMT6s) adjusted for creatinine (Graham *et al*., 1998). aMT6s is the primary urinary metabolite of melatonin. A complete overnight urine sample was used to estimate overnight melatonin production, normally about 85-90% of total 24-hour production. A post-work urine sample, taken on the same day as the post-work blood sample, was used to estimate work time melatonin blood levels. The overnight creatinine-adjusted aMT6s levels were, on average, about 5 times higher than the post-work creatinine-adjusted aMT6s levels. Noonan *et al*. state that the correlations between overnight creatinine-adjusted aMT6s and amyloid beta levels were not significant. No data were provided. However, post-work creatinine-adjusted aMT6s levels were negatively correlated with both the Aβ_{1-42} and the Aβ_{1-42}/ Aβ_{1-40} post-work levels. The Spearman correlation coefficients were -0.22 (p=0.08) and -0.21 (p=0.10), respectively. With adjustment for age and physical work, the correlation with Aβ_{1-42} was marginally stronger (-0.25, p=0.057). The timing of the urine sample with respect to the blood sample appears to be important. Table 4 provides the Spearman correlations, adjusted for age and physical work, based on the time difference between blood and urine samples, which were all obtained after the blood draw. Some of the workers had their urine sample in the early evening. It is clear that the correlation is strongest when the samples are taken close to one another in time.

  In an unadjusted analysis, the post-work creatinine-adjusted aMT6s levels were split into tertiles. Subjects in the highest tertile had the lowest levels of Aβ_{1-42}, Aβ_{1-40}, and Aβ_{1-42}/Aβ_{1-40} (Table 5). However, subjects in the middle tertile had higher levels than subjects in the lowest tertile.

- In an *in vitro* study, Del Giudice *et al.* (2007) used human neuroglioma cells (H4/APPswe), which stably overexpress a specific human mutant amyloid precursor protein (APP, to examine the effect of ELF MF exposure. ELF MF or sham exposure was 3.1 mT (31,000 mG) for 18 hours. Total Aβ and total $A\beta_{1\text{-}42}$ production was statistically significantly elevated among the ELF MF exposed cells compared to the cells with sham exposure. No gross morphological changes or changes in viability were observed in the ELF MF exposed cells. The 3.1 mT exposure level is 2-3 orders of magnitude higher than the highest occupational mean exposures. The authors state that such high levels were administered because occupational exposures are "much more prolonged than the one described in our experimental setting". There was no indication that any longer duration exposure at lower levels was studied.

B. Alzheimer's Disease Alternative/Complementary Pathway: Lowered Melatonin Production

<u>Conclusion</u>: *There is considerable in vitro and animal evidence that melatonin protects against AD. Therefore it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD.*

Several *in vitro* and animal studies indicate that melatonin may be protective against AD and thus low or lowered melatonin production may be a risk factor for AD. These studies have generally found that supplemental melatonin has the following effects:

- the neurotoxicity and cytotoxicity of Aβ is inhibited, including mitochondria (Pappolla *et al.*, 1997, 1999, 2002; Shen YX *et al.*, 2002a; Zatta *et al.*, 2003; Jang *et al.*, 2005);
- the formation of β-pleated sheet structures and Aβ fibrils is inhibited (Pappolla *et al.*, 1998; Poeggeler *et al.*, 2001; Skribanek *et al.*, 2001; Matsubara *et al.*, 2003; Feng *et al.*, 2004; Cheng and van Breemen, 2005);
- the profibrillogenic activity of apolipoprotein E ε4, an isoform conferring increased risk of AD, is reversed (Poeggeler *et al.*, 2001);
- oxidative stress *in vitro* and in transgenic mouse models of AD is inhibited if given early (Clapp-Lilly *et al.*, 2001a; Matsubara *et al.*, 2003; Feng *et al.*, 2006), but not necessarily if given to old mice (Quinn *et al.*, 2005);
- survival time is increased in mouse models of AD (Matsubara *et al.*, 2003);
- oxidative stress and proinflammatory cytokines induced by $A\beta_{1\text{-}40}$ in rat brain are reduced *in vitro* and *in vivo* (Clapp-Lilly *et al*, 2001b; Shen YX *et al.*, 2002b; Rosales-Corral *et al.*, 2003);
- the prevalence of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ in the brain is decreased in young and middle aged mice (Lahiri *et al.*, 2004);
- memory and learning is improved in rat models of AD pathology (Shen YX *et al.*, 2001; Weinstock and Shoham, 2004), but not necessarily in Aβ-infused rat models (Tang *et al.*, 2002).

Note that transgenic mouse models of AD mimic senile plaque accumulation, neuronal loss, and memory impairment. See Pappolla *et al.* (2000), Cardinali *et al.* (2005), Srinivasan *et al.* (2006), Cheng *et al.* (2006), and Wang and Wang (2006) for reviews. Thus, chronic low levels of melatonin production may be etiologically related to AD incidence.

C. Epidemiologic Studies of Alzheimer's Disease and ELF MF Exposure

<u>Conclusion</u>: There is strong epidemiologic evidence that exposure to ELF MF is a risk factor for AD. There are seven studies of ELF MF exposure and AD. Six of these studies are more of less positive and only one is negative. The negative study has a serious deficiency in ELF MF exposure classification that results in subjects with rather low exposure being considered as having significant exposure. There are insufficient studies to formulate an opinion as to whether radiofrequency MF exposure is a risk factor for AD.

C.1. Introduction

First, it is necessary to point out that there are no case-control studies of melatonin as a risk factor for AD. This is primarily because AD results in a precipitous decline in melatonin production due to the destruction of specific neuronal structures and therefore it is inappropriate to use "current" melatonin production of cases as a surrogate estimate of the pre-AD melatonin production. Also there have yet to be any longitudinal studies of melatonin production. This is probably because neither urine nor blood have been collected appropriately to measure nocturnal melatonin production.

If MF exposure is a true risk factor, there are several problematic areas in evaluation and comparison of epidemiologic studies related to occupational MF exposure and Alzheimer's disease, particularly the following.

1. Diagnosis – false positive diagnoses will bias the odds ratio estimator towards 1.0
2. Occupational exposure assessment – inclusion of subjects with low exposure in the "exposed" categories likely biases the odds ratio estimator towards 1.0
    - Definition of MF exposure – published studies have differing definitions of MF exposure, potentially resulting in "exposure" categories with significant proportions of subjects with low exposure
    - Cut-points for non-exposure/exposure categories – some studies use numerical estimates of exposure developed from earlier exposure studies (job exposure matrices) in certain occupations and use average estimates and/or low cut-points to determine "medium" exposure
    - Ever versus never exposed – at least one study used ever exposed, with a low threshold for exposure
    - Categorized occupational data – categorized data from governmental databases leads to relatively large variation in "exposure" within occupational categories, which results in subjects with low exposure being classified as having been exposed.

Table 6 provides the data on the percentages of MF exposed subjects in the published studies to date. There is a wide range of percentages, due primarily to variation in exposure definition, use of average or mean job-specific estimates, and secondarily to the use of varying job exposure matrices. Table 7 provides the odds ratio estimates of studies discussed in some detail below. The studies which used death certificates or other non-expert databases for the identification of AD cases are not included in Table 7.

The role of seamstresses among workers with high occupational MF exposure in the two *et al.* studies (1995, 1996b) and the Davanipour *et al.* study (2007) is discussed.

C.2. **Death Certificates-Governmental Databases: Alzheimer's Disease Diagnosis**

The use of death certificates or governmental databases to identify AD cases is certainly problematic. False positive diagnoses tend to bias the OR estimator towards 1.0. Most diagnoses of AD have been and still are made by physicians who are not experts in AD, and who seldom have sufficient clinical time to make a proper diagnosis. The determination of dementia and subsequent differential diagnosis of AD by someone other than an expert has a high false positive rate. In addition, many physicians do not think that AD is a "cause of death", which results in an increase in the false negative rate.

Therefore the recent "positive" Feychting *et al.* (2003), Håkansson *et al.* (2003), and Park *et al.* (2005) studies and the "negative" Savitz *et al.* (1998a,b) and Noonan *et al.* (2002b) studies have been excluded from the discussion below of individual studies. The Johansen *et al.* study (2000) has also been excluded because it depended upon the clinical hospital discharge diagnoses of an historical cohort to determine a "diagnosis" of "presenile" AD or "dementia". Evidently, in that study, late-onset (age at least 65) AD was included under "dementia". (It should be noted that Johansen *et al*. found an increased risk of "dementia", but not "presenile" AD, associated with higher MF exposure.)

C.3. **MF Exposure Assessment Rates and Analytic Results**

The Sobel *et al.* (1995, 1996b), the Davanipour *et al.* (2007), and the Harmanci *et al.* (2003) studies have followed nearly the same protocol for MF exposure assessment and classification into low, medium and high MF occupations. In these studies, medium exposure was defined as mean MF occupational exposure above 2 mG, but less than 10 mG, or intermittent exposures above 10 mG, while high exposure was defined as mean MF exposure above 10 mG or intermittent exposures above 100 mG. The rates of medium or high (M/H) exposure in these studies are considerably lower than the rates in the Feychting *et al.* (1998a), Graves *et al.* ((1999), Qiu *et al.* (2004), and Savitz *et al.* (1998b) studies and somewhat lower than the Feychting *et al.* (2003) study. The remaining three studies (Häkansson *et al.*, 2003; Savitz *et al.*, 1998a; Johansen, 2000) utilized subjects from electrical industries and therefore understandably have high rates of MF exposure. (See Table 6 for these rates.)

Thus, it is likely that a substantial percentage of MF "exposed" subjects in 4 of the 6 comparable studies (Feychting *et al.*, 1998a; Graves *et al.*, 1999; Qiu *et al.*, 2004) (Table 7) had a high rate of somewhat minimal exposure in the "exposed" category, due to classification methodologies, compared to the "exposed" categories in the Davanipour *et al.* (2007), Harmanci *et al.* (2003), and the Sobel *et al.* (1995, 1996b) studies. This would tend to lead to an OR estimate closer to 1.0 in the 4 former studies.

C.3.1. **Sobel *et al.* (1995) Study – Positive Study**

The initial publication of an apparent association between AD and having worked in occupations with likely MF exposure consisted of three case-control studies, two from Helsinki, Finland, and one from Los Angeles, USA (Sobel *et al.*, 1995). Control groups varied: the first case-control study analyzed used VaD patients; the second (and largest study) used non-neurologic hospital patients; and the third (and second largest study) used non-demented well subjects. The study-specific ORs were 2.9, 3.1, and 3.0, while the combined OR was 3.0 (95% CI = [1.6 – 5.4], $p < 0.001$), with no confounder adjustments necessary. The occupational information was apparently primarily related to the last occupation, e.g., judge, high ranking military officer. A total of 386 cases and 575 controls was analyzed in these studies. 9.3% of the cases and 3.4% of the controls were judged to have had an occupation with likely medium or high MF exposure. Among women, 31 (5.3%) were exposed to M/H occupational MF, of whom 29 (95%) were seamstresses, who were classified as having high exposure based on measurements taken during the study. Seamstresses have subsequently been shown to have very high MF exposures (e.g., Hansen *et al.*, 2000; Kelsh *et al.*, 2003; Szabó *et al.*, 2006).

C.3.2. **Sobel *et al.* (1996b) and Davanipour *et al.* (2007) Studies – Positive Studies**

These two studies utilized the databases of the nine (9) State of California funded Alzheimer's Disease Diagnosis and Treatment Centers (ADDTC). Sobel *et al.* (1996b), the second published study of occupational MF and AD, used the Rancho Los Amigos (RLA) ADDTC database. There were 316 cases and 135 controls. Twelve percent (12%) of the cases and 5.3% of the controls had had a medium or high "primary" exposed (MF) occupation. The Davanipour *et al.*, 2007) study used the databases of the other 8 ADDTCs. Seven and one-half percent (7.5%) of the cases and 3.8% of the controls had had a medium or high MF "primary" occupation. Among the women in the RLA ADDTC study, 26 (8.4%) had M/H exposure, of whom 17 (65.4%) were seamstresses. In the Davanipour *et al.* study, among women, 50 (3.8%) had M/H MF exposure, of whom 34 (68%) were seamstresses. This difference is statistically significant ($p < 0.001$). Among the men in the RLA ADDTC study, 14.8% had a medium or high MF exposed occupation, while in the Davanipour *et al.* ADDTC study, 13.5% had a medium or high MF exposed occupation. This difference is not significant. It thus appears that the women in the combined populations from which the ADDTCs in the Davanipour *et al.* study have drawn their patients have a lower rate of MF exposed occupations than the population from which the RLA ADDTC draws its patients. This is not too surprising because Los Angeles has a large apparel manufacturing industry.

The OR (adjusted for age-at-onset, gender, and education) for medium or high MF exposure in the RLA ADDTC study was 3.9 (95% CI = [1.5 – 10.6], $p = 0.006$). The ORs for medium or high MF exposure in the Davanipour *et al.* ADDTC study were lower: 2.2 ($p < 0.02$; 95% CI = [1.2 – 3.9]) and 1.9 ($p < 0.04$; 95% CI = [1.04 – 3.6]), using age-at-exam and age-at-onset, respectively, plus gender and history of stroke in the model. These ORs are all statistically significant. In the two studies, the 95% CIs greatly overlap and, under the assumption of normality of the natural logarithms of the odds ratios estimators and a straightforward hypothesis test that the means of two independent normally distributed variables are equal, the null hypothesis that the corresponding ORs are equal cannot be rejected at the 0.05 level.

C.3.3. **Other AD and Occupational ELF MF Exposure Studies**

Studies with Positive Results

Qiu et al. (2004) *Study* Qiu *et al.* (2004) studied a Swedish cohort of 931 subjects, aged 75+ at baseline, followed for up to 7 years. Job history was usually obtained from the next-of-kin, but only after 4 years of follow-up. MF exposure assessment was estimated using previous occupational exposure studies, specific measurements (e.g., seamstresses and tailors), and expert opinion. During the follow-up period, 265 subjects developed dementia, with 202 receiving an AD diagnosis. Numerical exposure estimates were obtained using both the longest held occupation, last occupation, and any occupation. The estimated average daily MF exposure was used to classify individual exposure.

Exposure for a sample of seamstresses and tailors was measured at the head. They were classified as having low exposure. Exposures of seamstresses who used industrial sewing machines and workers who used home sewing machines likely were under estimated by Qiu *et al.* (2004): 5.5 mG for "industrial seamstresses" and 1.9 for tailors. Qui *et al.* only considered home sewing machines, which at the head had a mean exposure of 10 mG. For "industrial seamstresses, they assumed that 50% of the workday was at a 10 mG exposure and 50% was at background, 1 mG. This gives an average exposure of 5.5 mG. For tailors, they assumed that only 10% of the workday was spent sewing, so the mean exposure was 1.9 mG. There are several problems with this determination of exposure for seamstresses and tailors:

1. exposures to the head are among the lowest body exposures and are not necessarily the sole important exposure;
2. even in Sweden, it is unlikely that home sewing machines were exclusively used. It is more likely that most of the machines were industrial machines, which produce much higher fields constantly, even when sewing is not occurring;
3. seamstresses have exposure most of the workday;
4. ambient exposure levels in industrial settings have been measured at up to 6 mG (Sobel and Davanipour, unpublished Finnish data);
5. tailors would not make a living sewing only 0.8 hours per day.

Hansen *et al.* (2000) found that, at the side of the waist, mean full-shift exposure for industrial machines was approximately 30 mG, while Qiu used a figure of 10 mG. Based on unpublished measurements on AC home sewing machines, Sobel and Davanipour (1996c) found that exposures to the head were usually the lowest measurements, while the chest, pelvic area, thigh, knee, right arm and hand had much higher exposures (Table 8). In addition, foot pedals can produce high magnetic fields (Table 8). Also, AC/DC converters in the handles (right side) of computerized home sewing machines constantly produce high magnetic fields – about 75 mG at 2 inches away from the handle. The right hand, lower right arm, and knee regularly receive high exposures (Table 8). Thus, the 10% sewing time assumed by Qiu *et al.* (2004) does not mean that significant exposure is not over a longer time period. The biological plausibility of hypotheses discussed above provides an argument that exposure to other body parts may also be deleterious. The numbers or percentages of industrial seamstresses and/or home sewing machine workers were not provided by Qui *et al*.

Nevertheless, for the principal occupation, but not for the last occupation or cumulative lifetime exposure, Qiu *et al.* (2004) found statistically significant ORs: OR=2.3 (95% CI = [1.0 – 5.1]) for AD and OR=2.0 (95% CI = [1.1 – 3.7]) for any dementia for men with average exposures greater than 2 mG. For women, no increase in risk was found for the principal occupation, last occupation, and all occupations combined. The average lengths of time in the last and principal occupations were not provided. Thus, comparison with the Feychting *et al.* study (1998a) could not be made.

The proportions of subjects with at least 2 mG exposure were 28.2% for AD cases and 28.8% for controls for the principal occupation (Table 6). For all occupations combined, the proportions were higher. For men, with cases and controls combined, the proportions were 43.1% and 33.0%, respectively, for principal occupation and all occupations combined. For women, the proportions were 24.3% and 32.1%. In the Sobel *et al.* (1995, 1996b) and Davanipour *et al.* (2007) studies, the proportion of female cases and controls with medium or high exposure (considered above 2 mG) was only 5.5%, 80% of whom were seamstresses or had allied professions with significant MF exposure, e.g., cutter. Thus, in these three publications, the exposure category for women contained a higher percentage of subjects with very high exposure. This may explain the lack of findings among women. The occupations which were in the exposure categories 'at least 2 mG' (dichotomized exposure) or 'at least 1.8 mG' (trichotomized) were not provided by Qiu *et al.* (2004).

Harmanci et al. (2003) *Study* Harmanci *et al.* (2003) conducted a cross-sectional, population-based study of Alzheimer's disease by selecting a random sample of 1067 subjects at least age 70, among whom 1019 (96%) agreed to participate in the study. AD was determined in a two-step process: a screening exam using the Turkish version of the Mini-Mental State Exam (MMSE), followed by an expert clinical exam among those whose MMSE scored indicated cognitive impairment. Two hundred twenty three (223) were asked to have a clinical exam, and 155 (69.5%) agreed. Among the subjects with a "normal" score on the MMSE, 126 were randomly selected for a clinical examination. Among these 281 subjects, 57 were clinically diagnosed as having possible AD, and 127 were determined to be cognitively normal. These subjects were included in the case-control study. M/H MF exposed occupations were stenographers and typists, carpenters and joiners, metal molders and core makers, tailors, dressmakers, and hatters. Except for stenographers, these occupations were considered to result in medium or high MF exposure in the Sobel *et al.* (1995, 1996b) and current study. A stepwise backwards logistic regression analysis was used. Medium/high MF exposure occupations had an adjusted OR of 4.0, with a 95% CI of [1.02 – 15.78]. It is interesting to note that use of electrical residential heating was also a risk factor (OR = 2.8, 95% CI = [1.1 – 6.9]).

Feychting et al. (1998a) *Study* In the case-control study by Feychting *et al.* (1998a), MF exposure during the last occupation, but not during the longest held occupation, was a risk factor for dementia not caused by a single stroke. The last occupation was held an average of 24.8 years among cases and 25.9 and 25.1 years among subjects within the two control groups. Consequently exposure during the last occupation was over a significant period of time. Using the two control groups, the ORs for dementia were 3.3 and 3.8 with 95% CIs of [1.3 – 8.6] and [1.4 – 10.2] for occupations with geometric mean MF exposures estimated to be at least 2 mG. Housewives were excluded from the analyses. The ORs for Alzheimer's disease were somewhat lower (2.4 and 2.7). When the analysis was restricted to subjects aged 75 and below at onset or examination, the ORs (5.0 and 4.8) for AD were statistically significant. Also, for subjects of all ages with occupations likely to have resulted in an average MF exposure above 5 mG, the ORs for AD were both high, but significant for one referent group (OR = 8.3), and not for the other (OR = 4.1). The Feychting *et al.* study was small: 44 dementia cases had occupational data, 29 of whom were diagnosed with AD. 43% of the cases were in the MF exposed group, while 23% and 19% of the controls were in this exposure group. Given these high percentages, it is clear that some lower MF exposed occupations were classified in the exposed category than were classified in this study and the earlier Sobel *et al.* studies (1995, 1996b).

Study with Only Negative Results

Graves et al. (1999) *Study* Graves *et al.* (1999) studied 89 matched case-control pairs. Complete occupational histories were obtained. MF exposure in a given occupation was defined as having at least "probable intermittent exposures (a few minutes)" above 3 mG. A high exposure category was defined as exposure of "1 to several hours" above 3 mG. Two industrial hygienists rated the occupations. Thus, many exposed subjects likely had a low average exposure. 19.1% and 21.4% of the cases were considered to have been 'ever' exposed, while 21.4% and 22.5% of the controls were considered 'ever' exposed. An unknown number of subjects, classified as having experienced MF exposure, would not have been so classified in most or all of the other studies of neurodegenerative diseases or cancer. The estimated adjusted ORs for ‘ever’ having been exposed were 0.74 and 0.95, depending upon which industrial hygienist's classification was used (Graves *et al.*, 1999).

As noted above, the Feychting *et al.* (1998a) study found elevated odds ratios associated with the last occupation, and in the Sobel *et al.* studies (1995, 1996b) and the Davanipour *et al.* (2007) study, occupational information most likely related to the last occupation. Also, Feychting *et al.* (1998a) did not find an increased risk associated with measures which included earlier occupations, e.g., highest exposed occupation and longest held occupation. Qui *et al.* (2004) found elevated risk associated with the principal occupation for males. Consequently, 'ever' vs 'never' exposed, as used by Graves *et al.* (1999), may not be an appropriate comparison.

Graves *et al.* (1999) also used a cumulative exposure index, the weighted sum of the numbers of years in each occupation with the weights being 0, 1 and 2 for no exposure, only "intermittent exposures" above 3 mG, and exposure for "1 to several hours" above 3 mG, respectively. Using the non-zero cumulative index values, exposure was dichotomized at the median as 'low' or 'high'. Adjusted ORs for 'low' or 'high' cumulative exposure versus no exposure were also close to 1.0. The last or the primary occupation was not separately analyzed.

In summary, the non-significance of the ORs in the Graves *et al.* (1999) study may be due to three reasons: (1) less restrictive definitions of magnetic field exposure resulting in minimally exposed subjects being classified as having been 'ever exposed' or even highly exposed; (2) equal weight given to exposure during any age period, e.g., age 25-45 and age 45-65; (3) a cumulative exposure metric which equates what can be negligible exposure with significant exposure, e.g., negligible exposure for 20 years equals significant exposure for 10 years. In addition, there were no seamstresses among their subjects, who were from an HMO established primarily for union families. Seamstresses are seldom in a union.

D. Epidemiologic Studies of Alzheimer's Disease and RF Exposure

There are no studies of AD and RF to discuss. The single published epidemiologic study of RF and melatonin is discussed in Section II (Burch *et al.*, 2002).

IV. BREAST CANCER

Figure 2 provides a schematic outline of the areas of study providing evidence that ELF MF exposure can lead to breast cancer through an effect on melatonin production levels, and, of course, possible but unknown other pathways. Section references are provided in Figure 2.

There is now accumulating evidence that low melatonin production may increase the risk of breast cancer (BC). This evidence comes from *in vitro*, animal, and two longitudinal human studies. The *in vitro* and animal study literature is quite extensive, so only a highlight review is provided. There are numerous published case-control studies of residential and occupational MF exposure as a risk factor for breast cancer. No epidemiologic studies of radiofrequency MF exposures and breast cancer have been published, which do not include ELF MF exposure, and which have reasonable data on RF exposure.

For a review of melatonin from basic research to cancer treatment, see Vjayalaxmi *et al.*, 2002.

- *Conclusion: There is sufficient evidence from in vitro and animal studies, from human biomarker studies, from occupational and light at night studies, and a single longitudinal study with appropriate collection of urine samples to conclude that high MF exposure may certainly be a risk factor for breast cancer. Most of the residential MF exposure studies have been negative. This may be because "high" residential exposures are actually not very high. Individual exposures may be of importance, e.g., home sewing machines, hair dryers, AC/DC converters near the head of the bed, water pipes causing intermittent high exposures near living room or TV room sofas and easy chairs.*

A. *In Vitro* and Animal Studies Relating to Melatonin as a Protective Factor against Breast Cancer

A.1. *In Vitro* Studies Related to Prevention of Oxidative Damage; Comparative *in vivo* Studies with Vitamin C and Vitamin E

Melatonin has been found to neutralize hydroxyl radicals and to reduce oxidative damage in over 800 publications (Reiter et al., 1995; Tan *et al.*, 2002). Melatonin has also been shown to act synergistically with vitamin C, vitamin E and glutathione (Tan *et al.*, 2000) and stimulates the antioxidant enzymes superoxide dismutase, glutathione peroxidase and glutathione reductase (Reiter *et al.*, 2002).

- Using a cell-free system, Tan et al and others have demonstrated that melatonin neutralizes hydroxyl radicals more efficiently than does reduced glutathione Tan *et al.*, 1993a; Bromme *et al.*, 2000).
- Melatonin reduces oxidative damage to macromolecules in the presence of free radicals (Reiter *et al.*, 1997, 2001a). One mode of action is as a free radical scavenger (Reiter *et al.*, 2001b).
- Melatonin increases the effectiveness of other antioxidants, e.g., superoxide dismutase, glutathione peroxidase, and catalase (Antolin *et al.*, 1996; Kotler *et al.*, 1998; Pablos *et al.*, 1995; Barlow-Walden *et al.*, 1995; Montilla *et al.*, 1997).
- Melatonin has protective effects against ultraviolet and ionizing radiation (e.g., Vijayalaxmi *et al.*, 1995). Vijayalaxmi et al studied the effects of melatonin on radiation induced chromosomal damage in human peripheral blood lymphocytes (Vijayalaxmi *et al.*, 1996). Blood from human volunteers was collected before and after administration of a single 300 mg oral dose of melatonin. The post-administration samples of both serum and leukocytes had increased concentration of melatonin compared to the samples prior to melatonin administration. After gamma radiation and mitogen exposure, a sample of cells was cultured for 48-72 hours. Lymphocytes from the sample after melatonin was administered had significantly fewer chromosomal aberrations and micronuclei. Primary DNA damage was reduced. Vijayalaxmi et al hypothesized that melatonin, in addition to its hydroxyl radical scavenging, may also stimulate or activate DNA repair processes (Vijayalaxmi *et al.*, 1998).

Melatonin has been found to be a more potent protector from oxidative injury than vitamin C or vitamin E (micromoles/kg) in several *in vivo* studies (for a review, see: Tan *et al.*, 2002). Melatonin was also found *in vitro* to scavenge peroxyl radicals more effectively than vitamin E, vitamin C or reduced glutathione (Pieri *et al.*, 1994; Reiter *et al.* 1995), although melatonin is not a very strong scavenger of peroxyl radicals (Reiter *et al.*, 2001b).

A.2. **Animal Studies of Mammary Tumor Prevention with Melatonin**

Several studies have found that melatonin inhibits the incidence of mammary tumors in laboratory animals either prone to such tumors or exposed to a carcinogen (e.g., Tamarkin *et al.*, 1981; Shah *et al.*, 1984; Kothari *et al.*, 1984; Subramanian and Kothari, 1991a,b; Blask *et al.*, 1991). In 1981, Tamarkin et al found that supplemental melatonin, given on the same day as 7,12-dimethylbenz(alpha)-anthracene (DMBA) and continued for 90 days, lowered the incidence of mammary tumors from 79% in controls to 20% ($p<0.002$) in the melatonin treated Sprague-Dawley rats (Tamarkin *et al.*, 1981). When they treated pinealectomized rats with DMBA, the incidence of mammary tumors increased to 88%, indicating a possible effect on endogenous melatonin on tumor incidence. Similar results, but with somewhat different study designs, using female Holtzman rats given the carcinogen 9,10-dimethylbenzanthracene have been found (Shah *et al.*, 1984; Kothari *et al.*, 1984). Subramanian and Kothari studied the suppressive effect by melatonin in rats treated similarly with DMBA under varying light:dark schedules and time of melatonin administration in both intact and pinealectomized female Holtzman rats (Subramanian and Kothari, 1991a). They found that when administered during the initiation phase, melatonin only suppressed tumor development in intact animals. However, when administered during the promotion phase, melatonin had suppressive effects regardless of the presence or absence of the pineal gland. Subramanian and Kothari (1991b) also studied C3H/Jax mice and spontaneous mammary tumor development. Mammary tumors developed in 23.1% of mice provided with melatonin from 21 to 44 days of age, but in 62.5% of control mice ($p<0.02$). Furthermore, there was a decrease in serum 17-beta-estradiol levels in the melatonin treated mice ($p<0.05$). In a N-methyl-N-nitrosourea (NMU) model of hormone-responsive Sprague-Dawley rat mammary carcinogenesis, Blask *et al.* (1991) found that melatonin, given during the promotion phase, reduced the incidence of tumors and antagonized estradiol's stimulation of NMU-induced tumor incidence and growth. They, however, did not find a decrease in estradiol in the melatonin treated rats.

In two studies, Tan *et al.* (1993b, 1994) found that melatonin protected Sprague-Dawley rats from safrole induced liver DNA adduct formation. The protection was found at both physiological and pharmacological levels of supplementation. The level of protection was dose dependent. Intraperitoneal injection of paraquat causes lipid peroxidation, a decrease in total glutathione, and an increase in oxidized glutathione in Sprague-Dawley rats. Melchiorri et al found that melatonin inhibits these effects (Melchiorri *et al.*, 1995). In addition, melatonin and retinoic acid appear to act synergistically in the chemoprevention of animal model tumors (Teplitzky *et al.*, 2001) and *in vitro* systems (e.g., Eck-Enriquez *et al.*, 2000).

A.3. **Animal Studies Related to Prevention of Oxidative DNA Damage by Estradiol and Radiation**

Karbownik *et al.* (2001) found that melatonin protects against DNA damage in the liver and kidney of male hamsters caused by estradiol treatment. They also found that in the testes, estradiol did not increase DNA damage, but that melatonin was protective against the natural level of oxidative DNA damage, as indicated by 8-hydrodeoxyguanosine (8-oxodG) levels. Several studies have found that laboratory animals are protected by melatonin from lethal doses of ionizing radiation (e.g., Blickenstaff *et al.*, 1994; Vijayalaxmi *et al.*, 1999; Karbownik *et al.*, 2000). Vijayalaxmi *et al.* (1999) and Karbownik *et al.* (2000) investigated markers of oxidative DNA damage and found that significant decreases in these markers in the melatonin treated animals.

A.4. **Melatonin: Scavenger of $^{\bullet}OH$ and Other ROS**

Melatonin is a powerful, endogenously produced scavenger of reactive oxygen species (ROS), particularly the hydroxyl radical ($^{\bullet}OH$). Other ROS which melatonin scavenges include hydrogen peroxide (H_2O_2), nitric oxide ($NO^{\bullet}$), peroxynitrite anion ($ONOO^-$), hypochlorous acid (HOCl), and singlet oxygen ($^1O_2$) (Reiter, 1991; Tan *et al.*, 2000, Hardeland *et al.*, 1995; Antolin *et al.*, 1997; Stasica *et al.*, 1998). $^{\bullet}OH$ is produced at high levels by natural aerobic activity. ROS are also produced by various biological activities or result from certain environmental and lifestyle (e.g., smoking) exposures.

Hydrogen peroxide does not appear to react directly with DNA (Halliwell, 1998), but does undergo chemical reactions within the cell nucleus which produce $^{\bullet}OH$, e.g., with Fe^{+2}. On the other hand, $^1O_2$ readily oxidizes the guanine base. HOCl, $ONOO^-$, $NO^\bullet$ damage in various patterns (Halliwell, 1998).

However, $^\bullet OH$ is the most reactive and cytotoxic of the ROS (Halliwell *et al.*, 1986). $^\bullet OH$ appears not to be removed by antioxidative enzymes, but is only detoxified by certain direct radical scavengers (Tan *et al.*, 1999) such as melatonin.

Melatonin is found in every cell of the body and readily crosses the blood-brain barrier. It scavenges ROS at both physiologic and pharmacologic concentrations. In the literature, “physiologic” refers to blood level concentrations of melatonin, while “pharmacologic” indicates 2-3 orders of magnitude higher concentration. Recently, intracellular levels of melatonin, especially within the nucleus, have been shown to be naturally at “pharmacologic” levels for all cellular organelles studied to date (Maestroni, 1999; Reiter *et al.*, 2000).

Tan *et al.* (2002) review the underlying basis for melatonin’s scavenging of ROS, which is briefly discussed here. From the known structure-activity relationships, the reactive center of the interaction between oxidants and the melatonin molecule is its indole moiety. This is due to its high resonance stability and quite low activation energy barrier towards free radical reactions. In addition, the methoxy and amide side chains contribute significantly to melatonin’s antioxidant activity. The methoxy group in the C5 component of the molecule appears to prevent prooxidative activity. If this methoxy group is replaced by a hydroxyl group, under some *in vitro* conditions, melatonin may exhibit prooxidant capability. The mechanisms of melatonin’s scavenging ROS appear to involve the donation of an electron to form a melatoninyl cation radical or a radical addition at site C3 of the melatonin molecule. (There are other possibilities also.) All known intermediates generated by the scavenging of a ROS by melatonin are also free radical scavengers. This is known (by some) as the ‘free radical scavenging cascade reaction’, which allows one melatonin molecule to scavenge 4 or more ROS. (See Tan *et al.*, 2007, for details).

B. Longitudinal Human Studies of Low Overnight Melatonin Production as a Risk Factor for Breast Cancer

Conclusion: Two longitudinal studies have been conducted of low melatonin production as a risk factor for breast cancer. Neither study collected urine samples in an optimal manner to estimate the important component of melatonin production – overnight production. No published longitudinal study has collected complete overnight urine. However, one used first morning void, which is close to optimal, but the other had to use 24-hour collection, which hides possible non-circadian rhythm. The study with the first morning void was positive, the other was negative. Thus, there is some longitudinal evidence that low melatonin production is a risk factor for breast cancer.

There have been only two longitudinal studies of low melatonin production as a risk factor for breast cancer. Note that many breast cancers are associated with a decrease in melatonin production (Bartsch *et al.*, 1997). There is often a “rebound” after excision of the tumor, but it is not known if post-excision melatonin production is near the pre-tumor production level (Bartsch *et al.*, 1997). Thus, as with AD, it is not appropriate to use post-tumor melatonin levels in a case-control study of low melatonin as a risk factor for breast cancer.

DNA damage is the pathway through which normal cells become malignant. Thus, the greater the amount of DNA, the greater the probability of a malignant transformation and the development of a cancer. Davanipour *et al.* (2007) have conducted a study on the association between endogenous melatonin levels and oxidative guanine DNA damage among mothers and their oldest sampled daughters. The mothers' age range was 43-80, while the oldest daughter's age range was 18-51. Nearly all of the mothers, but few of the daughters were postmenopausal. Complete overnight urine samples were obtained. Creatinine-adjusted aMT6s and 6-hydrodeoxyguanosine (8-oxodG) were assayed. 8-oxodG is a measure of the level of oxidative DNA damage. Creatinine-adjustment is not necessary because the 8-oxodG level using complete overnight urine is a measure of the total repair of oxidized DNA guanine during the night. There was a statistically significant (p=0.02) inverse association between the level of nocturnal melatonin production (aMT6s/creatinine) and 8-oxodG for the mothers, but not for the daughters. Statistical adjustment was made for age and weight; however, there was little difference in the results with or without adjustment. The correlation between creatinine-adjusted aMT6s and 8-oxodG was 0.35 (p=0.01).

Positive Study

Schernhammer and Hankinson (2005) reported on the association between urinary melatonin levels and breast cancer risk in the Nurses' Health Study II. The study had collected first morning void urine samples prior to the diagnosis of any cancer in a sub-sample of the women in the study. Assays of aMT6s and creatinine for 147 women who developed invasive breast cancer, and 291 age-matched controls, plus 43 women who developed in situ breast cancer and 85 matched controls were analyzed. Analyses were based on quartiles of creatinine-adjusted aMT6s developed from the control data, with subjects in the lowest quartile as the referent group. (Thus, the analyses were conducted with a view that higher levels of melatonin production might be protective.) Unadjusted analyses, estradiol level adjusted analyses, and analyses adjusted for age-at-menarche, parity, age-at-first birth, family history of BC and benign breast disease, alcohol use, antidepressant use, and body mass index were conducted. It should be noted that low levels of melatonin are causally associated with earlier age-at-menarche (e.g., Cohen *et al.*, 1978; Sizonenko, 1987). Thus, inclusion of age-at-menarche in the adjustment is perhaps not appropriate. Analyses of cases and controls from the lowest and the highest quartile were statistically significant for each level of adjustment. The odds ratios (OR) were all 0.59. (In terms of risk associated with low melatonin production, the OR was 1/0.59 = 1.69.) Inclusion of the the cases with in situ breast cancer led to OR between 0.68 and 0.70. Significance levels were not provided. However, the 95% CI's for invasive breast cancer did not contain 1.0, while the 95% CIs when in situ breast cancer cases were included just barely contained 1.0.

** It should be noted that the first morning void, especially when the subject has had urine voids during sleep time, is not as good as complete overnight urine collection in estimating nocturnal melatonin production. **

Negative Study

Travis *et al.* (2004) conducted a study of melatonin and breast cancer using the Island of Guernsey or Guernsey III longitudinal study. This study recruited women for an eight and one-half year period, ending in 1985. During the follow-up period, 127 women developed breast cancer. Three hundred fifty three (353) controls were selected with matching based on age, recruitment date, menopausal status, day of menstrual cycle (if applicable) when the urine sample was obtained, and number of years post-menopausal (if applicable). Twenty-four (24) hour urine samples were collected. These samples were evidently not divided between overnight and other time-of-day sub-samples. None of the analyses (all cases-controls, only pre-menopausal cases-controls, or only post-menopausal cases-controls) showed any hint of an increase risk associated with low 24-hour melatonin production.

** It is unfortunate that the 24-hour urine samples were not subdivided by time of day. It is the nocturnal blood level of melatonin that is important. About 85%-90% of pineal melatonin is produced nocturnally. The circadian rhythm appears to be vital for the effects of melatonin in regulation of important biologic functions, including immune response. This particular problem with the study makes the results suspect. (See Hrushesky and Blask, 2004, for further details.) **

C. **No Case-Control Studies of Low Melatonin Production as a Risk Factor for Breast Cancer**

As mentioned previously, breast cancer itself often causes a decrease in melatonin production, e.g., Bartsch *et al.* (1997). It is therefore inappropriate to use current levels of melatonin production of breast cancer cases in a case-control study of whether low levels of melatonin are a risk factor for breast cancer, and none have been published.

D. **Light-at-Night and Night Shift Work Studies as a Risk Factor for Breast Cancer – Surrogates for Low Melatonin Production**

Conclusion: There is moderately strong evidence that both longterm light-at-night and night shift work increase the risk of breast cancer. Five (5) studies are reviewed, 4 of which are positive. The negative study did find an increased risk for light-at-night, but not shift work. This study classified subjects as having had rather short shift work as exposed. Only very few subjects had at least 8 years of shift work: 8 (1.6%) of cases and 19 (3.7%) of controls.

Several studies have found an increase in risk of breast cancer among women who have rotating night shift work or who otherwise experience light at night. Light at night (LAN) is well-known to cause a decrease in nocturnal melatonin production (e.g., Lewy *et al.*, 1980; Lowden *et al.*, 2004; Schernhammer *et al.*, 2004). Note that occupational studies of MF exposure (Section E, below) have included jobs with night shift work, e.g., flight attendant and radio/telegraph operators.

<u>Positive Studies</u>

- Lie *et al.* (2006) studied the occurrence of breast cancer among Norwegian nurses. All data were obtained from government registers. Among a cohort 44,835 nurses, who graduated from a 3-year nursing program between 1914 and 1980 and who were alive on January 1, 1953, or born after this date, 537 breast cancer cases which occurred between 1960 and 1982 were identified. (1960 was chosen because that was the first year for which fertility data were available.) Four (4) controls, alive and cancer free, for each case were selected from the nurse cohort, matched by year of birth (± 1 year). Controls were required to have graduated or started their initial job no later than the year the corresponding case was diagnosed with BC. Number of years of night shift work was estimated from work history and work locations. Statistical adjustments in OR estimates included total employment time and parity. The OR for 30+ years of night shift employment versus 0 years, was 2.21 ($p<0.05$), 95% CI = [1.10 – 4.45]. The p-value for trend was 0.01. When the analysis was limited to nurses aged 50+, the OR was 2.01 ($p>0.05$), 95% CI = [0.95 – 4.26]. The number of cases without night shift work was only 50 for all ages, and was 29 for nurses over age 50. The number of cases with at least 30 years of night shift work was 24. (No case below age 50 had 30+ years of night shift work.)

- Schernhammer *et al.* (2001) examined rotating night shift work as a possible risk factor for breast cancer in the Nurses' Health Study. The total number of years in which a subject had worked rotating night shifts of at least 3 nights per month was obtained in 1988. The sample was quite large: 31,761 nurses had not had any years meeting the night shift criterion; 40,993 had had 1-14 years; 4,426 had had 15-29 years; and 1,382 had had 30+ years. During the following 10 year period, 2,441 incident cases of breast cancer were identified. Compared to nurses who had had no qualifying years, the adjusted relative risk (RR) for nurses with 30+ years of rotating night shift work was 1.36, with a 95% CI of [1.04 – 1.78]. All subjects with 30+ of rotating night shift work were post-menopausal Analyses were also conducted within pre- and post-menopausal groups. The RR and 95% CI were the same for 30+ years of exposure, because the number of nurses with no exposure decreased slightly (from 925 down to 801). While not statistically significant, perhaps due to sample size, pre-menopausal nurses who had at least 15 years of shift work had an adjusted RR of 1.34, 95% CI = [0.77 – 2.33], essentially the same RR as post-menopausal women (RR=1.36, 95% CI = [1.04 – 1.78]) who worked night shift for at least 30 years. There were only 14 pre-menopausal nurses with 15+ years of exposure. The trend in RR for increasing years of exposure was statistically significant for post-menopausal nurses and all nurses. Adjustments were made for age, weight change between age 18 and menopause, and many other variables associated with breast cancer. The increase in risk was almost totally due to hormone-receptor positive breast cancers. This was the first prospective night shift and breast cancer study.

- Davis *et al.* (2001b) studied 813 breast cancer patients, aged 20-74, and 793 controls. The controls were obtained through random digit dialing and were frequency matched by 5-year age intervals. Lifetime occupational history, bedroom lighting, and sleep habits were obtained by interview for the 10 years prior to diagnosis. Not sleeping during nocturnal periods (when melatonin production is usually at its peak) had an OR of 1.14 for each night per week. The 95% CI was [1.01 – 1.28]. Night shift work had an OR of 1.6, 95% CI = [1.0 – 2.5]. There was a significant upward trend (p = 0.02) in the OR with increasing years and more hours per week in night shifts. Statistical adjustments were made for parity, family history of BC, oral contraceptive use (ever), and recent (but discontinued) use of hormone replacement therapy.

- Hansen (2001) studied BC risk among younger Danish women whose work was mostly at night. All women born between 1935 and 1959, and 30-54 years of age, were identified though the Danish Cancer Registry. The number of such women was 7,565. One control per case was randomly selected from the Danish Central Population Registry. Controls were (i) living, (ii) apparently cancer free, and (iii) working before the date of diagnosis of the corresponding case. Work history was obtained from the Danish pension fund database. No work history was found for 530 cases, so the number of case-control pairs for the study was 7,035. Using a national survey (1976) of women and working conditions, 4 occupational categories were identified in which at least 60% of the female employees so some work at night. These were manufacturing of beverages, land transport services, catering, and air transport services. For hospitals, furniture manufacturing, water transport services, and cleaning services, between 40% and 59% of the women work some night shifts. Comparisons were made between occupations in which 60%+ of the women work night shifts and occupations in which less than 40% work night shifts. Only occupations within 5 years of diagnosis were considered. This limit was based on suspected induction time for breast cancer. To be placed in the "exposed" category a women had to have worked at least 6 months in a night shift occupation. Statistical adjustments were made for age, social class, ages at birth of first and last child, and parity. The OR for all "exposed" occupations was statistically significant ($p<0.05$): OR=1.5, 95% CI = [1.3 – 1.7]. For women who worked at least 6 years in "exposed" occupations, the OR was 1.7 ($p<0.05$). The results were essentially driven by the catering and air transport service occupations. (It should be noted that these two occupations may also result in higher MF exposure, compared to manufacture of beverages and land transport services.) The authors state that "(w)hen the 5-year induction time was ignored, the ORT decreased marginally".

<u>Negative Study</u>

- O'Leary *et al.* (2006) studied night shift work, light-at-night and BC in Long Island, NY, as part of the Electromagnetic Fields and Breast Cancer on Long Island Study (EFBCLIS) Group. There were 487 cases and 509 population-based controls, frequency matched to the expected age distribution of the cases in the study. These subjects had to have participated in the earlier Long Island Breast Cancer Study Project (LIBCSP). Each case had to have lived in the same home for at least 15 years prior to the diagnosis of breast cancer, while each control had to have lived in the same residence for at least 15 years prior to recruitment. Cases had to have had their BC diagnosis within the 12 month period beginning August 1, 1996. Controls were concurrently recruited. The LIBCSP had collected, via direct interview, complete job history information, including shift work – all jobs held for at least 6 months beginning at age 16, full time or part-time. The EFBCLIS repeated the job history interview, without the shift work information, for the period 15 years prior to the date of BC diagnosis (cases) or recruitment (controls). Military assignments were included. Light-at-night information was obtained by interview, and included information about sleep hours, frequency and length of having lights on during sleep time for the 5 year period prior to the reference date.

Exposure to shift work was defined as ever having had a job (≥ 6 months, either part or full time) with at least 1 day per week of shift work, during the 15 years prior to the reference date. Sub-groups were defined as follows: ever had an evening shift job; ever had an overnight shift job; ever had an evening shift, but never an overnight job; ever had an overnight shift; but never an even shift job. Statistical analyses were adjusted for reference date, parity, family history of BC, education, history of benign breast disease.

For any of the various categories of shift work during the 15 years prior to the reference date, there was no elevated risk of BC. However, 'any overnight shift work' had a statistically significant OR below one. The referent group included subjects with a jobs having less than 1 shift work day per week. Such a job could have been held for many years. The OR for at least 8 years of overnight shift work was statistically significantly below 1. For light-at-night within 5 years prior to the reference date, the only statistically significant finding was an OR = 1.65 for waking up and turning on lights at least 2 times per night versus doing so no more than 3 times per month.

The authors conclude that their study "provides mixed evidence for the light-at-night hypothesis". Analyses of shift work within 5 years of the reference date, the "induction" period used by Hansen (2001), were not presented. Overnight shift work was in the work history of only 26 cases and 50 controls; a duration of at least 8 years of overnight shift work was experienced by only 6 cases and 19 controls. Thus, the effective, "exposed" sample size was quite small. Information as to when this shift work occurred relative to the reference date was not provided.

E. Occupational Case-Control Studies of MF Exposure as a Risk Factor for Breast Cancer

<u>Conclusion</u>: *There is rather strong evidence from case-control studies that longterm, high occupational exposure to ELF magnetic fields is a risk factor for breast cancer. Six (6) independent studies are reviewed. Four (4) have positive conclusions, while two (2) are negative. The latest study is particularly strong. The two negative studies have serious shortcomings in exposure classification and come from the same research group.*

There have been several case-control studies of occupations with more or less high MF exposure and the risk of breast cancer. These studies have been generally positive, in the sense that there appears to be an increased risk. Earlier studies generally lack appropriate exposure information (e.g., Wertheimer and Leeper, 1994).

Positive Studies

- Peplonska *et al.* (2007) have conducted a large, population-based, case-control study of breast cancer and 73 occupational categories. All incident cases of cytologically or histologically confirmed breast cancer among women aged 20-74 in Warsaw and Lódź, Poland, in 2000-2002 were identified. 2,502 controls were randomly selected using the Polish Electronic System of Population Evidence, which maintains records on all citizens of Poland. Controls were matched to cases by city of residence and age ± 5years. A structured questionnaire was completed by 79% of the cases and 69% of the controls. The questionnaire included items related to demographics, reproductive and menstrual history, hormone use history, physical activity, occupational history for all jobs held at least 6 months, smoking, alcohol use, diet, cancer history in female relatives, medical and screening history, prenatal exposures, and history of weight and height development. Occupational information included job title, start and stop dates, employer, company products and/or services, work activities and duties, physical activity related to work, passive smoking, and exposures to a list of chemicals. The study was funded by the U.S. National Cancer Institute (NCI) and managed by Westat (Rockville, MD).

  Statistical adjustment was made for age, age-at-menarche (≤ 12; 13-14; ≥ 15), menopausal status; age-at-menopause, parity ≤ 1; 2; ≥ 3), body mass index (< 25; 25-30; ≥ 30 kg/m^2), first degree female family history of BC, education (< high school; high school; some college or professional training; college degree), previous mammographic screening, and city of residence. Oral contraceptive use, marital status, tobacco and alcohol use, age-at-first full term birth, breastfeeding, recreational and occupational history were not used for adjustment in the final analyses because they had “little impact” on the results.

  In the primary analyses, for each specific job category/industry, the referent group consisted of all subjects who did not work in that job/industry for at least 6 months. For each specific “white-collar” occupation, additional analyses using all other white-collar jobs as the referent group were conducted. This was thought to provide at least a partial account for socio-economic factors not accounted for by education. Similar blue-collar job analyses were not conducted. Several job categories containing occupations with elevated MF exposure had statistically significantly elevated ORs.

  <u>** These ORs were significantly elevated despite the fact that all other occupations with elevated MF exposure were placed in the referent group. **</u>

  ELF MF exposure was determined using a job exposure matrix developed within NCI for a brain cancer study. No, low, medium and high categories were developed by “experienced industrial hygienists”. (No reference was provided.) The highest MF exposure category of all jobs for an individual was used in analyses. 99% of the high exposed subjects were so ranked due to employment as machine operators and tenders in the textile apparel and furnishing industry. Information on which occupations were classified as low or medium MF exposure were not provided.

** <u>It should be noted that (1) 'tenders' generally provide maintenance to machinery and (2) operators of machines other than sewing machines, e.g., cutters, both have lower MF exposure than seamstresses. **</u>

The OR for high MF exposure versus no exposure was significant: OR = 1.5, 95% CI = [1.1 – 2.0]. For low exposure, the OR was also significant: OR = 1.2, 95% CI = [1.0 – 1.5]. For medium exposure the OR was also 1.2, but the 95% CI was [0.9 – 1.5]. Additional data analyses were not provided. The OR for high exposure among textile apparel machine operators and tenders is in line with the statistically significantly increased OR for seamstresses in the Forssén *et al.* (2005) study (see below under "negative studies") discussed below. In the Forssén *et al.* study (2004), seamstresses were classified as having medium-low MF exposure.

Specific ORs for occupations classified (surprisingly and for some likely incorrectly) as having high (as opposed to low or at most medium) MF exposure by Forssén *et al.* (2004) (see below) were calculated: cooks (OR=1.0); computer scientists (OR=1.3); computer and peripheral equipment operators (OR=0.7); data entry keyers (OR=0.3); dentists (OR=0.6); dental nurses (OR=1.0); counter clerks and cashiers (OR=1.1); and telephone operators (OR=0.9).

- Labréche *et al.* (2003) studied occupational ELF MF exposure and post-menopausal breast cancer. Cases and controls were identified through pathology department records at 18 hospitals in Montreal, Canada. These hospitals treat most of the breast cancer cases in the area. Age was restricted to 50-75 at the time of initial diagnosis of primary BC. Cases had to be residents of the region and the diagnosis had to have been in 1996 or 1997. Controls had one of 32 other cancer diagnoses and were frequency matched by age and hospital. The following cancers were excluded: liver, intrahepatic bile duct, pancreas, lung, bronchus, trachea, brain, central nervous system, leukemia, lymphoma, and non-melanoma skin cancer, but not gastrointestinal (Schernhammer *et al.*, 2003) or colorectal cancer (Bubenik, 2001).

  Complete occupational history, including task descriptions, and other personal information was obtained by personal interview, either of the subject or a surrogate if the subject was deceased or otherwise unavailable. Specialized occupational questionnaires were used for specific occupations, including sewing machine operators, cooks and nurses. The development of these questionnaires was lead by Jack Siemiatycki. See, for example, Siemiatycki *et al.* (1991, 1997). ELF MF exposures were estimated from detailed descriptions of tasks, equipment used, and the work environment by industrial hygienists intimately familiar with Montreal workplaces. The MF exposure categories and primary occupations were as follows: no exposure (< 2 mG; low exposure (2-5 mG, "typical jobs", including VDT operators, electric typewriter operators); medium exposure (5-10 mG; denturists, machinists); and high exposure (≥ 10 mG; sewing machine operators, textile workers). The industrial hygienists "confidence" in each subject's exposure assessment was obtained as definitely no exposure, or low, medium, and high confidence of exposure.

Exposures to benzene, perchloroethylene, and alphatic aldehyes, chemicals found in the textile industry, were also considered.

Statistical adjustments were made for age at diagnosis, family history of breast cancer, education, ethnicity, age-at-bilateral oophorectomy, age-at-menarche, age-at-first full-term pregnancy, oral contraception use, duration of HRT, total duration of breast feeding, alcohol use, smoking, and body mass index, as appropriate. Adjustment was also made for proxy versus personal responses because proxies tend to report fewer jobs. In addition, duration of employment in the textile industry was an adjustment variable. As mentioned previously, adjustment for age-at-menarche is probably not appropriate due to melatonin's causal relationship with age-at-menarche.

In addition to the categorical analyses, the number of hours of medium or high exposure was used as a risk factor. The number of hours from the lower limit of the second quartile to the upper limit of the third quartile of medium/high exposure was 6000 hours. ORs were presented for a difference of 6000 hours.

All analyses, e.g., no exposure vs ever exposed, prior to 10 years before diagnosis, or before age 35, were non-signficant and non-elevated except for the following ones, adjusted for textile industry employment and other factors:

- ✓ No exposure vs medium-to-high exposure – OR = 1.90, 95% CI = [0.99 – 3.85];
- ✓ 6000 hour increase in medium-to-high exposure – OR = 1.21, 95% CI = [0.97 – 1.49];
- ✓ 6000 hour increase in medium-to-high exposure prior to 10 years before diagnosis – OR = 1.31 ($p<0.05$);
- ✓ 6000 hour increase in medium-to-high exposure prior to age 35 – OR = 1.54 ($p<0.05$).

The significant results appear to be primarily due to MF association with progesterone positive and/or estrogen positive breast cancers.

The use of a 10 year lag eliminates exposure periods which may be too near the diagnosis time to be etiologically relevant. The analysis of exposures prior to age 35 identifies the time period when the development of female breast cells appears to cease.

The use of textile industry employment (yes/no) or length of time in the textile industry, as appropriate, as a covariate provides some adjustment for chemical exposures. Thus, the increase in the ORs when adjustment was also made for textile industry employment relates to MF exposure.

Finally, controls also had cancer. While many of the excluded cancers may conceivably have ELF MF as a risk factor, some of the non-excluded ones may also. This is especially true if the melatonin hypothesis is correct. Thus, the OR estimates may be biased towards 1.

- Kliukiene *et al.* (1999, 2003, 2004) and Tynes *et al.* (1996) studied occupational MF exposure and breast cancer among Norwegian women in general and radio and telegraph operators in particular. These were follow-up studies. A population-based cohort of 1.1 million women was developed using the 1960, 1970, and 1980 censuses. All women were working at the time of enrollment and had a potential for occupational MF exposure. The follow-up period was from 1961-1992. Date of birth, and census information about occupation and socioeconomic status was obtained. Incidence of breast cancer was obtained from the Cancer Register of Norway. Out-migration information was obtained.

  For the countrywide, all occupations study (1999), MF occupational exposure assessment was not optimal, but was as follows. The first method used expert opinion. An expert panel, using written guidelines, decided whether a given occupation had MF exposure above 1 mG for than 4 hours per week, between 4 and 24 hours per week, or more than 24 hours per week. Occupations were identified by a 3-5 digit industry code and a 3-digit occupation code. For cumulative exposure, the mean of each of the three (3) levels of exposure were used: 2 hours; 14 hours, 32 hours (based on a 40 hour week). It was assumed that each subject was in the same occupation from census to census, unless she died, emigrated or turned age 65.

  The second method used the Swedish job exposure matrix used in the Forssén *et al.* (2000) study (below), which was constructed from observations of male workers. Cumulative exposure was categorized as below 9 mG-years, between 9 and 14 mG-years, between 14 and 30 mG-years, and above 30 mG-years. Exposure was also classified by number of work hours of exposure above background (1 mG): below 900 hours; 900-999 hours; 1000-1999 hours; 2000 or more hours.

  Poisson regression, with adjustment for age, time period, and socioeconomic status, was used to estimate the relative risk (RR) of breast cancer. 22,543 breast cancer cases were diagnosed during the follow-up period. In the total cohort and the two sub-cohorts for those below or at least 50 years of age at inclusion in the cohort (Kliukiene *et al.*, 2004), the RRs were statistically significantly above 1.0 for each category of number of exposed hours, with below 900 hours as the reference category. For each cumulative exposure category above the reference category (below 9 mG-years, the RR for the total was statistically elevated. For the two sub-cohorts, the RRs were significantly elevated for the 9–14 and 14–30 mG-years categories. For the 30+ mG-years category the RRs were elevated, but lower bounds of the 95% CIs were 0.98 and 0.99.

  These studies did not have very good occupational data.

  For the radio and telegraph operators studies, the same cohort and occupational determination method was used. The Kliukiene *et al.* (2003) study was identical to the Tynes *et al.* (1996) study, except for a longer follow-up. By the end of May 2002, there were 99 breast cancer cases among the 2619 radio and/or telegraph operators in the cohort. The standardized incidence ratio was 1.30, 95% CI = [1.05 – 1.58].

A nested case-control study was also conducted, using the 99 BC cases and 4 controls per case matched on year of birth ± 5 years for cases born prior to 1920 and ± 1 year for cases born in 1920 or later. It was an update of an earlier study by Tynes *et al.* (1996). The reference category consisted of subjects (all radio and/or telegraph operators) who were not registered in the Norwegian Seamen Registry, i.e., had no history of working on merchant ships. MF exposure was not particularly explicit. It seems to have been assumed that that women who had no history of working on merchant ships had lower MF exposure (ELF and radiofrequency) than those with a history of such work. Spot ELF MF and radiofrequency MF measurements in the radio/telegraph rooms of 2 and 3 ships, respectively, were performed. RF magnetic and electric fields were below the detection level of the instruments at the operator’s desks. ELF magnetic fields varied from 0.2 mG to 60 mG at the operator’s desks. However, the highest exposures were only to the stretched out leg. “Normal” exposure to the body varied from 1 mG to 2 mG. Thus, exposure was certainly not high.

Tertiles of cumulative exposure at sea were used in the statistical analyses, with adjustment for age-at-first birth and parity. Detailed job histories on each ship were available for each ‘exposed’ subject. For each ship, the amount of time spent in the radio/telegraph room was estimated by an experienced researcher. A rank of 1-3 was assigned: 1 – ‘long voyage’ for tankers or dry-cargo ships with longer stays as sea; 2 – ‘many calls’ for trade ships with several loading and discharge ports; 3 – larger passenger ships. Increasing rank implies increasing percentage of time spent in the radio/telegraph room. Exposure was then calculated by summing the product of the number years of service on ships of each rank by the rank of the ships.

Analyses were conducted for total exposure, and for total exposure with lag times of 10 and 20 years prior to BC diagnosis. Analyses were conducted for (1) all cases and controls, for cases and controls below age 50 in the reference year, and for cases and controls at least age 50 in the reference year, and (2) ER+ and ER- cases.

No OR was statistically significant for any analysis without consideration of ER status. However, there was a statistically significant increasing trend in the ORs over cumulative exposure categories in the analyses for all cases, cases younger than 50, and cases at least age 50. There was also a significant upward trend for a 10 year lag time using all cases. The ORs for the highest exposure category were all elevated, but not significant perhaps because of the sample size.

For analyses by ER status, the only significant finding was for ER- cases, age 50+ in the highest exposure category. There were elevated ORs for all exposure categories for all ER- cases, and for the highest exposure category for ER+ cases and for ER+ cases below age 50.

The authors concluded that “occupational exposure to electromagnetic fields increases the risk of (female) breast cancer” (Kliukiene *et al.*, 2003).

- Loomis *et al.* (1994) investigated BC mortality among female electrical utility workers. This study used U.S. national death certificate information, 1985-1989, to identify cases and controls (without leukemia or brain cancer as a cause or contributing cause of death) and occupations. There were 27,814 women with breast cancer and sufficient occupational information, of whom 68 had an “electrical” occupation. There were 110,750 controls, of whom 199 had an “electrical” occupation. The primary factor limiting the sample size was the availability of occupational information. It should be noted that use of occupational data from death certificates is far from optimal. Statistical adjustments were made for age, ethnicity, and social class. Loomis *et al.* found an elevated risk associated with having an electrical occupation recorded on the death certificate: OR=1.38 ($p<0.05$). The only specific occupation with a statistically significant elevated risk was telephone installers, repairers and line workers: OR=2.17. Electrical engineers and electrical technicians had ‘elevated’, but not significant risk estimates (OR=1.73 and 1.28). On the other hand, air traffic controllers, telephone operators, data keyers, computer operators, computer programmers did not have ‘elevated’ risk estimates.

  In a letter commenting on the Loomis *et al.* paper, Kantor *et al.* (1995) analyzed essentially the same data set, with the inclusion of data from 1984. They used an industrial hygienist to estimate the probability of occupational ELF MF exposure or video display terminals (0, low, medium or high) among white and black women. The ORs were statistically significant (but not particularly high) for medium or high probability of exposure for both white and black women. When the hygienist actually categorized the level of ELF MF exposure, only medium exposure was associated with a statistically significant OR. High exposure had somewhat lower ORs.

<u>Negative Studies</u>

- Forssén *et al.* (2005) published a case-control study of occupational MF exposure and breast cancer. This study may be considered influential, unless reviewed in detail. So considerable detail is provided.

  > The Forssén *et al.* (2005) study found no association between occupational MF exposure, as determined by Forssén *et al.* (2005) , and breast cancer. The study is singled out because (1) it is essentially well designed, and (2) has a completely inappropriate ELF MF occupational classification scheme based on either non-representative workers in specific occupations or what should be considered quite suspect individual measurements (Forssén *et al.*, 2004). Many occupational groups which are generally considered to contain higher MF exposed occupations have been classified as low or medium-low exposure.

** Forssén *et al.* (2005) did find that seamstresses had statistically significantly elevated risk of breast cancer. However, they classified seamstresses as having medium-low MF exposure. **

Forssén *et al.* (2005) used newly collected exposure data for occupations in which women commonly work (Forssén *et al.*, 2004). The exposure study assessed occupations identified within the Swedish 1980 census. Forty-nine (49) specific occupational titles were identified. Volunteers working in each of these occupations were then ascertained by methods which are not specified. Personal 24-hour ELF MF measurements were obtained on what was presumably supposed to be a typical 24-hour day, using a dosimeter worn at the waist. The volunteers kept a diary so that time periods at work, at home, and elsewhere could be identified. The number of subjects with measurements by occupation ranged from 5 to 24. The total number of subjects measured was 471. There were only 5 observations for Seamstresses, and 5 Radio and Television Assemblers and Repairwomen. The workday measurements were used for classification purposes. In the epidemiologic study of breast cancer, 4 categories of exposure were used: Low (< 1 mG); Medium-Low (1-1.9 mG); Medium-High (2-2.9 mG); and High (≥ 3 mG). The occupations in the categories above ‘low’ are provided in Table 9. The arithmetic rate of change measure was also calculated. Seamstresses and Radio and Television Assemblers and Repairwomen were both classified as medium-low exposed occupations. The 5 seamstresses measured for exposure had their own small businesses and did not work in apparel manufacturing. They evidently also did not do much sewing. They spent 55% of their workday in fields below 1 mG and only 15% in fields above 3mG. This is only an average of 1 hour and 12 minutes of ‘high’ exposure during a working day. In the two counties in Sweden in which both the measurement study and the breast cancer case-control study were performed, there was almost no apparel manufacturing (Forssén *et al.*, 2004; personal communication, M. Feychting, 2007). Still, it is difficult to imagine such low exposures among women who actually work as seamstresses.

The cases and controls were obtained from all women who were employed at any time between 1976 and 1999, based on any of the censuses between 1960 and 1990, in either Stockholm or Gotland counties, Sweden. Subjects entered the study in either 1976 or their 15th birthday, which ever came first, and were followed through 1999 or to the date of their initial breast cancer diagnosis. Cases were identified through the Regional Cancer Registry in Stockholm. The referent year was the year of the case’s diagnosis. Controls were selected randomly by age and calendar year, apparently matched to cases. Cases could not also be controls. Both cases and controls had to be living in Stockholm or Gotland counties during the referent year. All information, including occupational history, was obtained from registries. 20,400 cases and 116,227 controls were enrolled in the study. Varying numbers of cases and controls were used in the analyses, depending on the availability of occupational and other data. Statistical adjustment was made for age, referent year, parity, and socioeconomic status.

For statistical analyses, exposure was assessed in various ways: (1) MF exposure for the occupation closest to the time prior to the referent year; (2) MF exposure at the most recent census which was at least10 years prior to the referent date; (3) MF exposure at the most recent census when the subject was at least age 35. Analyses were also carried out by (4) splitting the study period at 1985, by (5) only using subjects who either always had low exposure or ever having had high exposure, and by (6) defining low exposure as a median less than 1 mG and a third quartile of less than 1.7 mG and high exposure as a median greater than 2.5 mG and a first quartile including 1.7 mG. With these definitions, high exposed occupations were cashiers, working proprietors in retail trade, air stewardesses, dental nurses, cooks, post office clerks, and kitchen maids. No time latency period was used in the analyses related to (3).

There were no significant or elevated adjusted ORs for analysis (1) using the 4 categories of exposure, either for all BC cases, ER positive cases, or ER negative cases, for age below or at least 50. The referent group had MF exposure below 1 mG. There were no significant or elevated adjusted ORs for analysis (1) using low versus high (separated) exposure categories defined by (6), above.

Finally, in a series of analyses based on exposure 10+ years before the referent year, before age 35 for post-menopausal women, referent year before or after 1985, maximum point exposure, rate of change, and proportion of time exposure was above 3 mG, only a single adjusted OR was significant. The significant OR=0.87 and was for medium-high MF exposure among post-menopausal women before age 35.

It is thus fair to say that Forssén *et al.* (2005) found no relationship between their assessment of MF exposure and breast cancer. The authors do recognize that "(t)he major concern in the study is exposure misclassification".

Their job exposure classification is at odds with other classifications. Forssén *et al.* (2004, 2005) have classified Dental Nurses, Cashiers in Retail Stores and Restaurants, Working Proprietors in Retail Trade, Cooks, and Air Stewardesses as high MF exposure occupations. None of these occupations would be classified as having high MF exposure in any other classification scheme. The common cut-point for high exposure is 10 mG. Cashiers, cooks, and air stewardesses may at times have medium or high exposure, depending on (1) the exposure from scanners, (2) the exposure from microwave ovens, mixers, other motorized kitchen equipment, and (3) the exposure time from sitting near electrical panels on takeoff and landing and in the airplane's kitchen areas.

> <u>** Forssén *et al.* should conduct a sub-study to determine the actual environment in which the seamstresses in their study worked, the type of machines used (industrial, home; AC or DC operation), and the percent of time spent actually sewing. They also should conduct a study of seamstresses in general in Stockholm and Gotland counties and the in-migration rates. Also, the authors note an occupational category labeled 'textile occupations', which certainly includes seamstresses, but is otherwise undefined in the paper. Textile occupations need to be specified and studied individually, as was done by Hansen *et al.*, 2000. It is important to determine</u>

whether the "seamstresses" in the Forssén *et al.* (2005) study have fundamentally different levels of exposure than seamstresses in other studies.**

The only significant occupational finding in this study related to seamstresses. Two analyses were conducted related to seamstresses (Table 10), probably because their exposure assessment was so at odds with every other series of exposure measurements of seamstresses. First, the OR for 'textile occupations', undefined in the paper, versus low MF exposed occupations was 1.37, 95% CI = [1.11 – 1.68]. Second, the OR for 'textile occupations' versus all other occupations, regardless of MF exposure assessment, was 1.33, 95% CI = [1.10 – 1.62]. The authors state that their results "suggest that the increased risk for breast cancer in these occupations might be related to some exposure other than magnetic fields".

'Textile occupations' were not defined, but could certainly have included a multitude of occupations with quite varying chemical exposures, and generally medium or high MF exposures. However, none of the 49 occupational categories, other than seamstress, used in the study appear to relate to textile occupations, if sales and administration are excluded.

The numbers of seamstresses as cases or controls in the study are not provided. However, in the AD studies by Sobel and Davanipour (1995, 1996, 2007), approximately 2% of the controls were seamstresses. Thus, there may have been at least 2000 seamstresses among the controls. Assuming that most, if not all women in "textile occupations" were seamstresses, and based on the OR of "textile occupations" vs MF exposure below 1 mG, the number of seamstresses with BC in the study can be estimated as approximately 475. Rough calculations indicate that if seamstresses are reclassified as having high MF exposure (> 3 mG), the adjusted OR for high occupational MF versus low occupational MF exposure would be about 1.10 and statistically significant. It is worth repeating that the Forssén *et al.* (2004) occupational classification for high MF exposure is (1) not as high as usual and (2) measured workday exposures are unusual for such occupations.

- Forssén *et al.* (2000) conducted an earlier case-control study of occupational and residential MF exposure and breast cancer. The cohort from which the study population was obtained consisted of all Swedish residents who lived within 300 meters of a (high power, 220 or 400 kilovolt) transmission line for at least one year between 1960 and 1985 and were at least age 16 sometime in the period. Subjects in this group living further away from transmission lines essentially had no exposure from such lines. Cases were identified through cancer registries. Controls were randomly selected and matched by age group, residence in the same parish at the time of diagnosis of the case and in the same type of house (single-family/apartment further than 300 meters from the same power line. (The parish/power line criteria were relaxed for 95 cases; a control could not be found for 7 cases.) Residential exposure was calculated from the MF generated by power lines. Occupation information was obtained from census data. An older job-exposure matrix was used to assess occupational MF exposure. Low (< 1.2 mG), medium (1.2 – 1.9 mG), and high (≥ 2.0 mG) exposure categories were selected, based on quartiles. Exposure greater or equal to 2.5 mG was also considered.

Statistical adjustments were made for the matching variables. Only occupational exposure immediately prior to the diagnosis of BC and only residential exposure at the time of diagnosis was used in the analyses. No information concerning occupations of the subjects was provided. It is unlikely that seamstresses were included in the analyses.

<u>No significant findings were identified.</u>

Of 1767 cases and 1766 controls, only 711 and 709, respectively, had residential exposure information, only 744 and 764 had occupational exposure information, and only 197 and 200 had both types of exposure information. For the actual analyses of occupational exposures, with matching variable adjustment, there was complete information for only 440 cases and 439 controls. For analyses using both occupation and residential exposures, and matching variables, there was complete information for only 87 cases and 83 controls.

F. Residential Case-Control Studies of MF Exposure as a Risk Factor for Breast Cancer

Residential MF exposure studies and BC have either used wire configuration coding, proximity to high voltage lines, various protocols of room measurements, or a combination of these methods. These studies have generally not found any increased risk of breast cancer (e.g., Feychting *et al.*, 1998; Davis *et al.*, 2002; London *et al.*, 2003; Schoenfeld *et al.*, 2003). Residential studies have measured actual magnetic fields only in current homes of cases and controls, thus homes which might be etiologically relevant are often or usually without actual measurements. Wire configurations and proximity to high voltage lines were at times used for surrogate measures of exposure related to previous homes. Each of these three methods of assessment of the level of exposure leads to significant classification errors. In addition, residential exposures are, almost always, surely relatively low. Individualized exposure, due for example to home sewing, sitting or sleeping near a panel of circuit breakers, sitting near a water pipe (e.g., in the floor or ceiling), is not identified. For homes near high voltage lines, rooms can have dramatically different ambient levels of MF. For these reasons, these studies are not relevant to the purposes of this review.

G. Radiofrequency Exposure and Breast Cancer

There are no epidemiologic studies of radiofrequency MF exposure and breast cancer which do not include ELF MF exposure and which have reasonable data on RF exposure, e.g., Kliukiene *et al.* (2003), above.

V. SEAMSTRESSES

> <u>Conclusion</u>*: Seamstresses are, in fact, one of the most highly MF exposed occupations, with exposure levels generally above 10 mG over a significant proportion of the workday. They have also been consistently found to be at higher risk of Alzheimer's disease and (female) breast cancer. This occupation deserves specific attention in future studies.*

Seamstress was the primary occupation among women with high MF exposure in the Sobel *et al.* (1995, 1996b) and Davanipour *et al.* (2007) studies related to AD. No other published AD study has evidently involved populations in which sewing was a somewhat common occupation. In the 5 independent case-control studies presented in the 3 Sobel & Davanipour papers, most of the high MF exposed women (cases and controls) were seamstresses. (Among women in these case-control studies, the Mantel-Haenszel AD odds ratio for seamstresses is 3.13, $p < 0.01$). Information about sewing as a hobby, which at least used to be common, was unavailable. Seamstresses have been shown to have very high ELF MF exposures (e.g., Szabó *et al.*, 2006; Kelsey *et al.*, 2003; Deadman and Infante-Rivard, 2002; Hansen *et al.*, 2000). Forssén *et al.* (2004) measured 5 "seamstresses" who owned independent small businesses and found what they classified as medium-low exposure – a mean of 1.7 mG. These 5 individuals used home sewing machines and evidently did not sew much. Peplonska *et al.* (2007), using a NCI occupational MF classification scheme found that, at least among women, nearly all high exposures occurred among textile machine operators and tenders. Both Forssén *et al.* (2005) and Peplonska *et al.* (2007) found statistically significantly elevated ORs for breast cancer among seamstresses/textile machine operators and tenders.

Sobel and Davanipour (1996c) measured ELF MF exposure from several home sewing machine models, both AC and DC models, to several parts of the body. The results are provided in Table 8. These results show that (1) high ELF MF exposure occurs to many parts of the body, (2) exposures vary by manufacturer, model, and even by machines of the same model, and (3) exposures depend on whether the machine operates by AC or DC current. For Alzheimer's disease and for breast cancer, it is not known where exposures may be most important. The peripheral Abeta hypothesis, if correct, would indicate that exposure to any location is important for AD. To affect pineal production of melatonin, it is not known whether exposure to the pineal gland is what is most important. For example, a majority of breast cancers causally lower pineal melatonin production. Because the melatonin production rebounds after excision of the tumor, the tumor itself must be secreting something that leads to the decline in melatonin production. Thus, it is conceivable that MF exposure may, at least in some individuals, also lead to the peripheral production of something that also causes a lowering of melatonin production. It is also not known whether MF exposure directly to the breast is etiologically important. Note that the right breast receives higher MF exposure from home sewing machines. No studies of right versus left breast cancer and use of home sewing machines have been published.

ACKNOWLEDGEMENT

The authors thank Dr. James Burch, University of South Carolina, for his careful review of the manuscript and his helpful suggestions and comments.

Figure 1: Hypothesized Biological Pathway from MF Exposure to AD Development (from Sobel & Davanipour, 1996a)

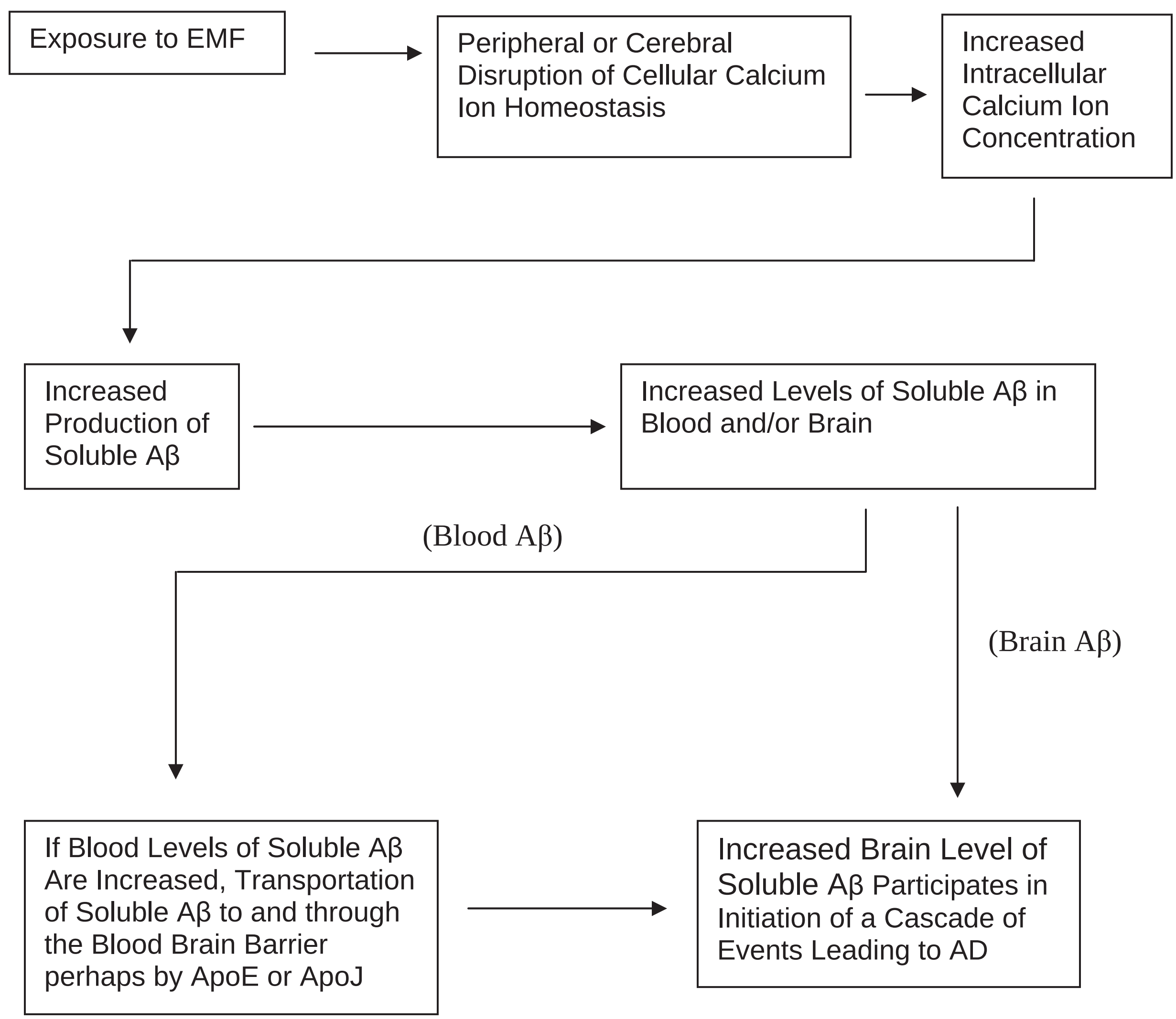
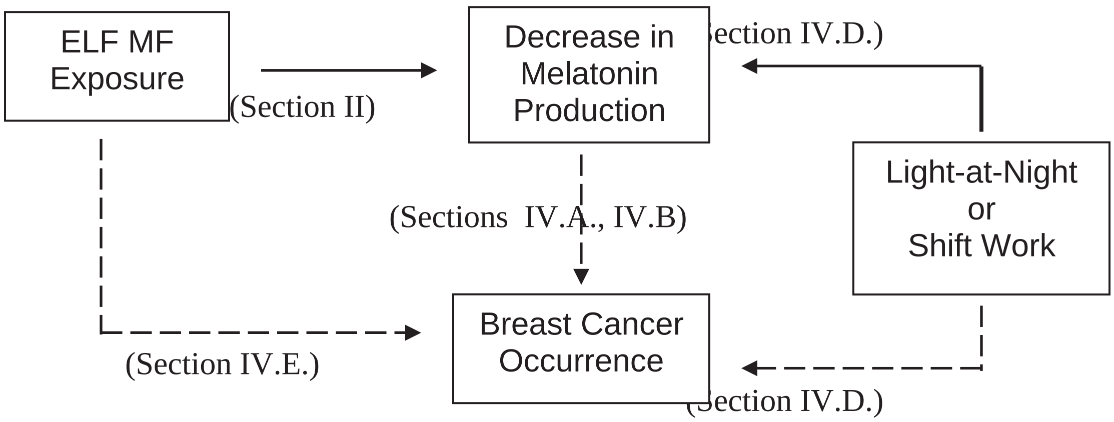


Figure 2: Outline of the Evidence that ELF MF Exposure Causes Breast Cancer through Decreases in Melatonin Production – with Section References



Note: Dashed lines indicate studies directly relating ELF MF exposure, light-at-night, or shift work to breast cancer occurrence.

Table 1: Baseline Data Results from the 1999 Mayeux *et al*. Paper: Means (Standard Deviation)

Variable	Cognitively Normal at Follow-Up	Developed AD (3.6 Year Average Follow-Up)
Sample Size (n)	105	64
Age	73.4 (5.3)	77.4 (5.9)[a]
Education	9.3 (4.6)	7.5 (3.8)[a]
$A\beta_{1\text{-}40}$ (pg/ml)	111.8 (44.1)	134.7 (46.4)[a]
$A\beta_{1\text{-}42}$ (pg/ml0	51.5 (42.0)	82.4 (68.8)[a]
$A\beta_{1\text{-}42}$/ $A\beta_{1\text{-}42}$	0.51 (0.41)	0.67 (0.56)[b]

<u>Notes</u>: Cognitively normal was determined at baseline by the global Cognitive Dementia Rating (CDR) scale with CDR=0 being normal. AD was diagnosed based on a CDR of 0.5 or 1.0, and clinical, functional and neuropsychological assessment as specified by the NINCDS-ADRDA criteria. [a] $p \leq 0.0001$; [b] $p < 0.05$.

Table 2: Baseline Data Results from the 2003 Mayeux *et al*. Paper: Means (Standard Deviation)

Variable	Cognitively Normal At Follow-Up	Developed AD (Up to 10 Year Follow-Up)
Sample Size (n)	365	86
Age	75.5 (5.9)	79.3 (6.6)[a]
Education	9.0 (4.6)	6.8 (4.5)[a]
$A\beta_{1\text{-}40}$ (pg/ml)	133.3 (61.9)	136.2 (46.7)[c]
$A\beta_{1\text{-}42}$ (pg/ml0	58.8 (32.9)	76.5 (59.8)[b]
$A\beta_{1\text{-}42}$/ $A\beta_{1\text{-}42}$	0.48 (0.3)	0.61 (0.53)[b]

<u>Notes</u>: Cognitively normal was determined at baseline by the global Cognitive Dementia Rating (CDR) scale with CDR=0 being normal. AD was diagnosed based on a CDR of 0.5 or 1.0, and clinical, functional and neuropsychological assessment as specified by the NINCDS-ADRDA criteria. [a] $p \leq 0.001$; [b] $p < 0.05$; [c] Not Significant.

Table 3: Post-Work Levels of $A\beta_{1-40}$, $A\beta_{1-42}$, $A\beta_{1-42}/A\beta_{1-42}$ by MF exposure among Electrical Workers in the Noonan *et al*. (2002a) Study

MF Exposure	$A\beta_{1-40}$ (pg/ml)	$A\beta_{1-42}$ (pg/ml)	$A\beta_{1-42}/A\beta_{1-42}$	Sample Size
< 0.5 mG	125	136	1.03	20
0.5 – 0.99 mG	137	163	1.11	25
1.0 – 1.99 mG	128	166	1.19	8
≥ 2.0 mG	156	262	1.46	7

Table 4: Correlation (Corr) between Post-Work Creatinine-Adjusted aMT6s and Amyloid Beta by Number of Minutes between Samples in the Noonan *et al*. (2002a) Study

Number of Minutes	Sample Size	$A\beta_{1-42}$ Corr	$A\beta_{1-42}$ p-Value	$A\beta_{1-40}$ Corr	$A\beta_{1-40}$ p-Value	$A\beta_{1-42}/A\beta_{1-40}$ Corr	$A\beta_{1-42}/A\beta_{1-40}$ p-Value
All Subjects	60	-0.25	0.057	-0.19	0.144	-0.23	0.080
≤ 90	46	-0.30	0.047	-0.22	0.154	-0.27	0.080
≤ 60	37	-0.37	0.027	-0.25	0.150	-0.37	0.029
≤ 30	23	-0.43	0.054	-0.28	0.224	-0.42	0.059

Table 5: Amyloid Beta Levels by Tertile of Post-Shift Creatinine-Adjusted aMT6s Levels in the Noonan *et al*. (2002a) Study

aMT6s/Cr Tertiles* (ng/mg)	$A\beta_{1-42}$ Mean**	$A\beta_{1-42}$ 95% CI	$A\beta_{1-40}$ Mean**	$A\beta_{1-40}$ 95% CI	$A\beta_{1-42}/A\beta_{1-40}$ Mean**	$A\beta_{1-42}/A\beta_{1-40}$ 95% CI
≤ 1.38	177	[112–258]	133	[111–156]	1.30	[0.86–1.74]
1.39–3.3	214	[120–334]	147	[125–170]	1.33	[0.85–1.90]
> 3.3	123	[58–180]	123	[108–139]	0.82	[0.49–1.26]

* n=60 subjects in each tertile
** geometric mean averaged over the work shift

Table 6: Percentages of Subjects with Medium to High MF Occupations Exposure

STUDY	CASES	CONTROLS
Sobel *et al.* (1995a)	9.3 %	3.4 %
Sobel *et al.* (1996b)	12.0 %	5.3 %
Davanipour *et al.* (2007)	7.4 %	3.8 %
Harmanci *et al.* (2003)	10.5 %	3.1 %
Feychting *et al.* (1998a)	43.0 %	23.0 % & 19.0 %#
Graves *et al.* (1999)	19.1 % & 21.4 %	21.4 % & 22.5 %^
Qiu *et al.* (2004)	28.2 %*	28.8 %*
	34.2 %**	42.7 %**
	Cases & Controls Combined	
Feychting *et al.* (1998)	11.1 %	
Håkansson *et al.* (2003)	80.5 % - likely exposed engineering industry workers	
Johansen *et al.* (2000)	56 % - electrical company workers	
Savitz *et al.* (1998a)	electric utility cohort – percentage not supplied	
Savitz *et al.* (1998b)	23.9 %	

Two control groups;
^ Two industrial hygienists
* Based on estimated daily exposure in principal occupation;
** Based on estimated daily exposure in all occupations

Table 7: Odds Ratios for the MF and AD Studies*

Study		Risk Estimate (OR)	95% CI	p-value
Sobel *et al.* (1995)	(late-onset; L vs M/H)			
		3.0	1.6 – 5.4	< 0.001
Sobel *et al.* (1996b)	(late-onset; L vs M/H)			
		3.9	1.5 – 10.6	0.006
Feychting *et al.* (1998)	(mostly late-onset; last occupation; by control group)			
	(exposure ≥ 2 mG)	2.4	0.8 – 6.9	--**
		2.7	0.9 – 7.8	--**
	(exposure ≥ 5 mG)	4.1	0.7 – 23.5	--**
		8.3	1.1 – 62.7	--**
Graves *et al.* (1999)	(late-onset; ever exposed)			
		0.95	0.4 – 2.4	--**
		0.74	0.3 – 2.4	--**
Harmanci *et al.* (2003)	(late-onset)	4.0	1.0 – 15.8	--**
	(exposure as defined in Sobel *et al.* (1995, 1996b))			
Qiu *et al.* (2004)	(age ≥ 75; exposure: ≥ 2 mG)			
	Men	2.3	1.0 – 5.1	--**
	Women	0.8	0.5 – 1.1	--**
Davanipour *et al.*, (2007)	(exposure as defined in Sobel *et al.* (1995, 1996b))			
	M/H vs L	2.2	1.2 - 3.9	< 0.02
	H vs L	2.7	0.8 - 9.1	< 0.11

* Studies use various types of controls and definitions of MF exposure. See text.
** p-values were not provided.

Table 8: Mean MF Exposures (mG) for Home Sewing Machines by Body Location: Continuous 2-Minute Measurements (Sobel & Davanipour, 1996c)

Sewing Machine	Background	Head	Breast		Pelvic Area	Thigh		Knee		Lower	Right	Foot Pedal
			Left	Right		Left	Right	Left	Right	Right Arm	Hand	
Alternating Current Machines (older machines)												
Bernina 811	0.6	18.6	5.6	12.9	26.9	11.7	90.1	8.9	13.5	251.1	57.0	86.1
Bernina 811	0.9	1.7	2.6	5.4	8.2	4.5	11.6	6.8	36.5	77.1	31.7	102.0
Bernina 817	0.6	8.4	9.6	23.5	41.9	19.1	30.6	9.2	35.4	724.6	135.6	NA
Bernina 817	1.2	12.1	14.2	33.9	51.0	10.3	588.5	8.8	125.7	753.0	132.4	NA
Brother 920D	0.7	2.4	2.1	2.3	1.1	1.3	1.5	1.9	2.3	8.5	16.0	6.2
Necchi Type 525	0.3	5.1	2.0	1.1	2.5	1.1	2.4	2.0	5.1	25.9	22.6	5.9
Sears Kenmore	0.2	1.2	1.9	4.9	5.5	2.2	5.3	2.5	15.8	26.0	17.9	13.8
Singer 625	0.3	4.6	3.6	5.6	5.5	3.9	6.6	6.4	17.2	...	...	...
Singer 5932	0.5	1.2	0.9	2.0	2.7	1.1	2.5	1.0	4.1	8.6	23.0	2.9
Singer 6212C	0.3	7.0	2.8	6.4	2.0	1.4	2.2	1.4	1.9	31.0	26.2	4.4
Viking Husqvarna 6020	0.8	1.5	1.3	1.5	2.7	1.4	2.0	3.1	9.1	5.9	24.9	62.3
White 1410	0.2	2.2	1.6	1.1	1.1	3.2	10.8	4.2	67.5	20.8	18.3	2.8
Direct Current Machines (newer machines)												
Bernina 1000	1.0	1.3	1.6	2.3	2.9	1.9	2.5	2.8	11.2	8.1	41.2	798.0
Bernina 1090S	1.0	1.2	1.6	1.6	1.7	1.2	1.3	1.5	7.7	3.3	22.9	1.0
Elna Diva 900	1.6	5.1	3.9	4.1	4.1	3.0	3.1	3.2	8.4	40.4	57.1	1.8
Singer 3317C	0.7	3.4	1.6	2.9	2.2	2.1	2.2	1.5	11.3	22.1	25.8	5.8
Singer 9015	0.7	2.5	1.9	3.3	4.9	1.7	4.3	2.1	26.2	7.0	28.9	2.3
Viking Husqvarna 500	1.0	3.7	2.7	5.0	3.9	1.8	2.8	2.7	13.8	24.9	39.4	1.1
Percent > 2.0 mG	0%	67%	50%	78%	83%	50%	89%	72%	94%	100%	100%	80%

Note: The Bernina 1000, Bernina 1090S, Elna Diva 900, Singer 3317C, Singer 9015 and Viking Husqvarna 500 were brand new. The Singer 5932, Singer 6212C, and Brother 920D were 3-10 years old. The Bernina 811 and 817 machines, the Sears Kenmore, the Singer 625 the Viking Husqvarna 6020 are probably at least 15 years old. Both the White and the Necchi are fairly old. NA = not applicable, i.e., there was no foot pedal. "..." = no measurements were taken, e.g., because of machine malfunction.

Percent > 2.0 mG	0%	67%	50%	78%	83%	50%	89%	72%	94%	100%	100%	80%

Note: The Bernina 1000, Bernina 1090S, Elna Diva 900, Singer 3317C, Singer 9015 and Viking Husqvarna 500 were brand new. The Singer 5932, Singer 6212C, and Brother 920D were 3-10 years old. The Bernina 811 and 817 machines, the Sears Kenmore, the Singer 625 the Viking Husqvarna 6020 are probably at least 15 years old. Both the White and the Necchi are fairly old. NA = not applicable, i.e., there was no foot pedal. "..." = no measurements were taken, e.g., because of machine malfunction.

Table 9: Classification of Occupations in Forssén *et al.* (2005)

Classification	Occupation	24-Hour Geometric Mean Average (mG)
High (≥ 3 mG)	Dental Nurse	3.0
	Air Stewardesses	3.0
	Cooks	3.1
	Working Proprietors in Retail Trade	3.4
	Cashiers in Retail Stores and Restaurants	4.5
Medium-High (2 – 2.9 mG)	Computer Operators	2.0
	Motor Vehicle Drivers	2.0
	Shop Managers	2.1
	Shop Assistants	2.1
	Hairdressers and Beauticians	2.1
	Bank Clerks	2.2
	Kitchen Supervisors	2.4
	Post Office Clerks	2.5
	Waitresses in Restaurants and School Kitchens	2.5
	Kitchen Maids	2.8
Medium-Low (1 – 1.9 mG)	Registered Nurses	1.0
	System Analysts and Programmers	1.2
	Telephone Operators	1.5
	Radio & Television Assemblers and Repairwomen	
	Seamstresses	1.6

Table 10: Odds Ratio Estimates for Textile Occupations in the Forssén *et al.* (2005) Paper

Comparison	OR	95% Confidence Interval
Textile Occupations vs Occupations with 24-Hour Exposure Below 1 mG	1.37	[1.11 , 1.68]
Textile Occupations vs All Other Occupations (Regardless of MF Exposure)	1.33	[1.10 , 1.62]

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SECTION 13

EVIDENCE FOR BREAST CANCER PROMOTION

(Melatonin Studies in Cells and Animals)

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July 2007

TABLE OF CONTENTS

Introduction

The subject of breast cancer and studies of melatonin has a long and rich history replete with destroyed scientific reputations and career-ending charges of misconduct of scientists who have contributed stellar scientific work that has proved extremely inconvenient for governmental agencies and military and industrial interests (Liburdy). References are given in each section below to facilitate locating the pertinent references for each section.

II. Melatonin and ELF-EMF

Evidence which supports a possible mechanism for ELF-EMF and breast cancer is the consistent finding (in five separate labs) that environmental levels of ELF-EMF can act at the cellular level to enhance breast cancer proliferation by blocking melatonin's natural oncostatic action in MCF-7 cells (Liburdy, 1993; Luben et al, 1996; Morris et al, 1998; Blackman et al, 2001; Ishido, et al, 2001). ELF-EMF levels between 0.6 and 1.2 μT have been shown to consistently block the protective effects of melatonin.

The series of papers reporting increased breast cancer cell proliferation when ELF-EMF at environmental levels negatively affects the oncostatic actions of melatonin in MCF-7 cells should warrant new public exposure guidelines or planning target limits for the public, and for various susceptible segments of the population.

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Girgert et al (2005) reported that *"the anti-estrogenic activity of tamoxifen is reduced in two subclones of MCF-7 cells under the influence of ELF/EMF to different extent. Dose-response curves of the growth-inhibitory effect of tamoxifen are shifted towards higher concentrations leading to a reduced growth inhibition at a given concentration. Our observations confirm results from a previous report describing a reduced inhibitory effect of tamoxifen at* 1^{-7} *M from 40% to only 17% by exposure to an EMF of 1.2 μT"* (Harland t al, 1997). Further, Girgert et al conclude that "*From a medical point of view, it is disturbing that maximal induction of cell proliferation by tamoxifen at a field strength of 1.2 μT is observed at concentration of* 10^{-6} *M. This is exactly the serum concentration achieved in BC patients under standard oral therapy."* (De Cupis et al, 1997).

The Girgert et al paper confirms prior findings that environmental level ELF-EMF inhibits the antiproliferative action of tamoxifen in MCF-7 human breast cancer cells. Four other papers reporting this effect include Liburdy et al, 1997; Harland et al, 1997; Harland et al, 1999; and Blackman et al, 2001).

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VII. Conclusions

Conclusion: The constellation of relevant scientific papers providing mutually-reinforcing evidence for an association between power-frequency electromagnetic fields (ELF-EMF) and breast cancer is strongly supported in the scientific literature.

Conclusion: ELF at environmental levels negatively affects the oncostatic effects of both melatonin and tamoxifen on human breast cancer cells. Numerous epidemiological studies over the last two decades have reported increased risk of male and female breast cancer with exposures to residential and occupational levels of ELF. Animal studies have reported increased mammary tumor size and incidence in association with ELF exposure.

Conclusion: ELF limits for public exposure should be revised to reflect increased risk of breast cancer at environmental levels possibly as low as 2 mG or 3 mG; certainly as low as 4 mG.

SECTION 14

EVIDENCE FOR DISRUPTION BY THE MODULATING SIGNAL

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I. Introduction

Modulation signals are one important component in the delivery of EMF signals to which cells, tissues, organs and individuals can respond biologically. At the most basic level, modulation can be considered a pattern of pulses or repeating signals which have specific meaning in defining that signal apart from all others. Modulated signals have a specific ‘beat’ defined by how the signal varies periodically over time. Pulsed signals occur in an on-off pattern, which can either be smooth and rhythmic, or sharply pulsed in quick bursts. Amplitude and frequency modulation involves two very different processes where the high-frequency signal, called the carrier wave, has a low-frequency signal that is superimposed on or ‘rides’ on the carrier frequency. In amplitude modulation, the lower-frequency signal is embedded on the carrier wave as changes in its amplitude as a function of time, whereas in frequency modulation, the lower-frequency signal is embedded as slight changes in the frequency of the carrier wave. Each type of low-frequency modulation conveys specific ‘information’, and some modulation patterns are more effective (more bioactive) than others depending on the biological reactivity of the exposed material. This enhanced interaction can be a good thing for therapeutic purposes in medicine, but can be deleterious to health where such signals could stimulate disease-related processes, such as increased cell proliferation in precancerous lesions. Modulation signals may interfere with normal, non-linear biological functions. More recent studies of modulated RF signals report changes in human cognition, reaction time, brainwave activity, sleep disruption and immune function. These studies have tested the RF and ELF-modulated RF signals from emerging wireless technologies (cell phones) that rely on pulse modulated RF to transmit signals. Thus modulation can be considered as information content embedded in the higher frequency carrier wave that may have health consequences beyond any effect from the carrier wave directly.

In mobile telephony, for example, modulation is one of the underlying ways to categorize the radiofrequency signal of one telecom carrier from another (TDMA from CDMA from GSM). Modulation is likely a key factor in determining whether and when biological reactivity might be occurring, for example in the new technologies which make use of modulated signals, some modulation (the packaging for delivery for an EMF ‘message’) may be bioactive, for example, frequencies are similar to those found in brain wave patterns. If a new technology happens to use brain wave frequencies, the chances are higher that it will have effects, in comparison, for example, to choosing some lower or higher modulation frequency to carry the same EMF information to its target. This chapter will show that other EMF factors may also be involved in determining if a given low-frequency signal directly or as a modulation of a radiofrequency wave can be bioactive. Such is the evolving nature of information about modulation. It argues for great care in defining standards that are intended to be protective of public health and well-being. This section describes some features of exposure and physiological conditions that are required in general for non-thermal effects to be produced, and specifically *to illustrate how modulation is a fundamental factor which should be taken into account in public safety standards*.

II. The Old Standards (Based on Heating and Electric Current Flow in Tissues)

It is universally accepted that radiofrequency radiation (RFR) can cause tissue heating and that extremely low frequency (ELF) fields, e.g., 50 and 60 Hz, can cause electrical current flows that shock and even damage or destroy tissues. These factors alone are the underlying bases for present exposure standards. EMF exposures that cause biological effects at intensities that do not cause obvious thermal changes, that is, effects via non-thermal mechanisms, have been widely reported in the scientific literature over the last several decades. The current public safety limits do not take modulation into account and thus are no longer sufficiently protective of public health where chronic exposure to pulsed or pulse-modulated signal is involved, and where sub-populations of more susceptible individuals may be at risk from such exposures.

III. Laboratory Studies

Published laboratory studies have provided evidence for more than 40 years on bioeffects at much lower intensities than cited in the various widely publicized guidelines for limits to prevent harmful effects. Many of these reports show EMF-caused changes in processes associated with cell growth control, differentiation and proliferation which are biological processes of considerable interest to scientists who study the molecular and cellular basis of cancer. EMF effects have been reported in gene induction, transmembrane signaling cascades, gap junction communication, immune system action, rates of cell transformation, and breast cancer cell growth. These reports have cell growth control as a common theme. Other more recent studies on brainwave activity, cognition and human reaction time lend credence to modulation (pulsed RF and ELF-modulated RF) as a concern for wireless technologies, most prominently from cell phone use.

Experimental results are described below to illustrate the influence of each EMF parameter, while also demonstrating that it is highly unlikely the effects are due to EMF-caused current flow or heating.

Several papers in the 1960s and early 1970s reported that ELF fields could alter circadian rhythms in laboratory animals and humans. In the latter 1960s, a paper reported that the EMF environment in planned space capsules could cause human response time changes, i.e., the interval between a signal and the human response (Hamer, 1968). Subsequent experiments by that research group were conducted with monkeys, and showed similar response time changes and also EEG pattern changes (Gavalas, 1970; Gavalas-Medici, 1976). The investigators shifted the research subject to cats and observed EEG pattern changes, ability to sense and behaviorally respond to the ELF component of RFR, and the ability of minor electric current to stimulate the release of an inhibitory neurotransmitter, GABA, and simultaneous release of a surrogate measure, calcium ions, from the cortex (Kaczmarek, 1973, 1974). At this time the investigators adopted newly hatch chickens as sources of brain tissue and observed changes in the release of calcium ions from in vitro specimens as a function of ELF frequency directly or as amplitude modulation (‘am’) of RFR (RFRam) (Bawin, 1975, 1976, 1978a, 1978b; Sheppard, 1979). Tests of both EMF frequency and intensity dependences demonstrated a single sensitive region (termed 'window') over the range of frequency and intensity examined. This series of papers showed that EMF-induced changes could occur in several species (human, monkey, cat and chicken), that calcium ions could be used as surrogate measures for a neurotransmitter, that ELF fields could produce effects similar to RFRam (note: without the 'am', there was no effect although the RFR intensity was the same), and that the dose and frequency response consisted of a single sensitivity window.

An independent research group published a series of papers replicating and extending this earlier work (Blackman et al., 1979, 1980a, 1980b, 1981, 1982, 1985, 1988a, 1988b, 1989, 1990; Joines and Blackman et al., 1981a, 1981b, 1986). These papers reported multiple windows in intensity and in frequency within which calcium changes were observed in the chick brain experimental systems under EMF exposure. Three other independent groups reported intensity and frequency windows for calcium, neurotransmitter or enolase release under EMF exposure of human and animal nervous system-derived cells in vitro (Dutta et al., 1984, 1989, 1992, 1994), of rat pancreatic tissue slices (Albert et al., 1980), and of frog heart (Schwartz et al., 1990) but not atrial strips in vitro (Schwartz et al., 1993). This series of papers showed that multiple frequency and intensity windows were a common phenomenon that required the development of new theoretical concepts to provide a mechanism of action paradigm.

Additional aspects of the EMF experiments with the chick brain described by Blackman and colleagues, above, also revealed critical co-factors that influenced the action of EMF to cause changes in calcium, including the influence of the local static magnetic field, and the influence of physico-chemical parameters, pH, temperature and ionic strength of the bathing solution surrounding the brain tissue during exposure. This information provides clues for and constraints on any theoretical mechanism that is to be developed to explain the phenomenon. These factors demonstrate that the current risk assessment paradigms, which ignore them, are incomplete and thus may not provide the level of protection currently assumed.

The detailed set of frequency and intensity combinations under which effects were observed, were all obtained from chickens incubated for 21 days in an electrically heated chamber containing 60-Hz fields. Tests were performed to determine if the 60-Hz frequency of ELF fields (10 volts per meter in air) during incubation, i.e., during embryogenesis and organogenesis, would alter the subsequent calcium change responses of the brain tissue to EMF exposure. The published papers (Blackman et al., 1988b; Joines et al., 1986) showed that the brain tissue response was changed when the field during the incubation period was 50 Hz rather than 60 Hz. This result is consistent with an anecdotal report of adult humans, who were institutionalized because of chemical sensitivities, were also responsive to EMF fields that were present in the countries where they were born and raised (Blackman, 2006). This information indicates there may be animal and human exposure situations where EMF imprinting could be an important factor in laboratory and epidemiological situations. EMF imprinting, which may only become manifest when a human is subjected to chemical or biological stresses, could reduce ability to fight disease and toxic insult from environmental pollution, resulting in a population in need of more medical services, with resulting lost days at work.

Fundamental exposure parameters that must be considered when establishing a mode (or mechanism) of action for non-thermal EMF-induced biological effects.

A. Intensity

There are numerous reports of biological effects that show intensity "windows", that is, regions of intensity that cause changes surrounded by higher and lower intensities that show no effects from exposure. One very clear effect is 16-Hz, sine wave-induced changes in calcium efflux from brain tissue in a test tube because it shows two very distinct and clearly separated intensity windows of effects surrounded by regions of intensities that caused no effects (Blackman et al., 1982). There are other reports for similar multiple windows of intensity in the radiofrequency range (Blackman et al., 1989; Dutta et al., 1989, 1992; Schwartz et al., 1990). Note that calcium ions are a secondary signal transduction agent active in many cellular pathways. These results show that intensity windows exist, they display an unusual and unanticipated "non linear" (non-linear and non-monotonic) phenomenon that has been mostly ignored in all risk assessment and standard setting exercises, save the National Council for Radiation Protection and Measurements. (NCRP) 1986 publication. Protection from multiple intensity windows has never been incorporated into any risk assessment; to do so would call for a major change in thinking. These results mean that lower intensity is not necessarily less bioactive, or less harmful.

Multiple intensity windows appeared as an unexpected phenomenon in the late 1970s and 1980s. There has been one limited attempt to model the phenomenon (Thompson et al., 2000). However, there are publications from two independent research groups showing multiple intensity windows for 50 MHz, 147 MHz, and 450 MHz fields when amplitude-modulated at 16 Hz using the calcium ion release endpoint in chicken brains, in vitro. The incident intensities (measured in air) for the windows at the different carrier frequencies do not align at the same values. However, Joines et al., (1981a, 1981b) and Blackman et al. (1981) noted the windows of intensity align across different carrier frequencies if one converts the incident intensity to the intensity expected within the sample at the brain surface, but correcting for the different dielectric constants in the samples at the different carrier frequencies. The uniqueness of this response provides a substantial clue to theoreticians but it is interesting that no publications have appeared attempting to address this relationship. It is obvious that this phenomenon is one that needs further study.

B. Frequency

Frequency-dependent phenomena are common occurrences in nature. For example, the human ear only hears a portion of the sound that is in the environment, typically from 20 to 20000 Hz, which is a frequency "window." Another biological frequency window can be observed for plants grown indoors. Given normal indoor lighting the plants may grow to produce lush vegetation but not produce flowers unless illuminated with a lamp that emits a different spectrum of light. Similarly, there are examples of EMF-caused biological effects that occur as a result of EMF of concern to us in a frequency-dependent manner that cannot be explained by current flow or heating. The examples include reports of calcium ion efflux from brain tissue in vitro at low frequency (Blackman et al., 1988a, 1988b) and at high frequency (Blackman et al., 1981; Joines and Blackman, 1981). The bioactive frequency regions observed in these studies have never been explicitly considered for use in any EMF risk assessments, thus demonstrating the incomplete nature of current exposure limits.

There are also EMF frequency-dependent alterations in the action of nerve growth factor (NGF) to stimulate neurite outgrowth (growth of primitive axons or dendrites) from a peripheral-nerve-derived cell (PC-12) in culture (Blackman et al., 1995, 1999; Trillo et al., 1996). The combined effect of frequency and intensity is also a common occurrence in both the sound and the light examples given above. Too much or too little of either frequency or intensity show either no or undesirable effects. Similarly, in low intensity EMF work, “islands” of effective combinations of intensity and frequency are surrounded by a “sea” of null effects (Blackman et al., 1988a). Although the mechanisms responsible for these effects have not been establish, the effects represent a heretofore unknown phenomenon that may have ramifications for risk assessment and standard setting. Nerve growth and neurotransmitter release that can be altered by different combinations of EMF frequencies and intensities, especially in developing organisms like children, could conceivably produce over time a subsequent altered ability to successfully or fully respond behaviorally to natural stressors in the adult environment; research is urgently need to test this possibility in animal systems.

Nevertheless, this phenomenon is ignored in the development of present exposure standards that rely primarily on biological responses to intensities within a relatively narrow band of frequencies, based on an energy deposition endpoint.

C. Static Magnetic Field

The magnetic field of the earth at any given location has a relatively constant intensity as a function of time. However, the intensity value, and the inclination of the field with respect to the gravity vector, varies considerable over the face of the earth. More locally, these features of the earth’s magnetic field can also vary by more than 20% inside man-made structures, particularly those with steel support structures. There are many reports of EMF-caused effects being dependent on the static magnetic field intensity (cf. Blackman et al., 1985) and of its orientation, with respect to an oscillating magnetic field

(Blackman et al., 1990; Blackman et al., 1996). One aspect common to many of these reports is that the location in the active frequency band is determined by the intensity of the static magnetic field. There have been many attempts to explain this phenomenon but none has been universally accepted. However, it is clear that if a biological response depends on the static magnetic field intensity, and even its orientation with respect to an oscillating field, then the conditions necessary to reproduce the phenomenon are very specific and might easily escape detection (cf. Blackman and Most, 1993). The consequences of these results are that there may be exposure situations that are truly detrimental (or beneficial) to organisms but that are insufficiently common on a large scale that they would not be observed in epidemiological studies; they need to be studied under controlled laboratory conditions to determine impact on health and wellbeing.

D. Electric & Magnetic Components

Both the electric and the magnetic components have been shown to directly and independently cause biological changes. There is one report that clearly distinguishes the distinct biological responses caused by the electric field and by the magnetic field. Marron et al. (1988) show that electric field exposure can increase the negative surface charge density of an amoeba, Physarum polycephalum, and that magnetic field exposure of the same organism causes changes in the surface of the organism to reduce its hydrophobic character. Other scientists have used concentric growth surfaces of different radii and vertical magnetic fields to determine if the magnetic or the induced electric component is the agent causing biological change. Liburdy (1992), examining calcium influx in lymphocytes, and Greene et al. (1991), monitoring ornithine decarboxylase (ODC) activity in cell culture, showed that the induced electric component was responsible for their results. In contrast, Blackman et al. (1993a, 1993b) monitoring neurite outgrowth from two different clones of PC-12 cells and using the same exposure technique used by Liburdy and by Greene showed the magnetic component was the critical agent in their experiments. EMF-induced changes on the cell surface, where it interacts with its environment, can dramatically alter the homeostatic mechanisms in tissues, whereas changes in ODC activity are associated with the induction of cell proliferation, a desirable outcome if one is concerned about wound healing, but undesirable if the concern is tumor cell growth. This information demonstrates the multiple, different ways that EMF can affect biological systems. Current analyses for risk assessment and standard setting have ignored this information, thus making their conclusions of limited value.

E. Sine and Pulsed Waves

Important characteristics of pulsed waves that influenced the number and characteristics of the sine wave representations include the following: 1) frequency, 2) pulse width, 3) intensity, 4) rise and fall time, and 5) the frequency, if any, within the pulse ON time. Chiabrera et al. (1979) showed that pulsed fields caused de-differentiation of amphibian red blood cells. Scarfi et al. (1997) showed enhanced micronuclei formation in lymphocytes of patients with Turner's syndrome (only one X chromosome) but no change in micronuclei formation when the lymphocytes were exposed to sine waves (Scarfi et al., 1996). Takahashi et al. (1986) monitored thymidine incorporation in Chinese hamster cells and explored the influence of pulse frequency (two windows of enhancement seen), pulse width (one window of enhancement seen) and intensity (two windows of enhancement seen followed by a reduction in incorporation). Ubeda et al. (1983) showed the influence of difference rise and fall times of pulsed waves on chick embryo development.

It is important to note that the frequency spectrum of pulsed waves can be represented by a sum of sine waves which, to borrow a chemical analogy, would represent a mixture or a soup of chemicals, anyone of which could be biologically active. Risk assessment and exposure limits have been established for specific chemicals or chemical classes of compounds that have been shown to cause undesirable biological effects. Risk assessors and the general public are sophisticated enough to recognize that it is impossible to declare all chemicals safe or hazardous; consider the difference between food and poisons, both of which are chemicals. A similar situation occurs for EMF; it is critical to determine which combinations of EMF conditions have the potential to cause biological harm and which do not.

Obviously, pulse wave exposures represent an entire genre of exposure conditions, with additional difficulty for exact independent replication of exposures, and thus of results, but with increased opportunities for the production of biological effects. Current standards were not developed with explicit knowledge of these additional consequences for biological responses.

F. Mechanisms

Two recent papers have the possibility of advancing understanding in this research area. Chiabrera et al. (2000) created a theoretical model for EMF effects on an ion's interaction with protein that includes the influence of thermal energy and of metabolism. Before this publication, theoreticians assumed that biological effects in living systems could not occur if the electric signal is below the signal caused by thermal noise, in spite of experimental evidence to the contrary. In this paper, the authors show that this limitation is not absolute, and that different amounts of metabolic energy can influence the amount and parametric response of biological systems to EMF. The second paper, by Marino et al. (2000), presents a new analytical approach to examine endpoints in systems exposed to EMF. The authors, focusing on exposure-induced lyphoid phenotypes, report that EMF may not cause changes in mean values of endpoints, but rather in variances in those same endpoints. They provide further evidence using immunological endpoints from exposed and sham treated mice (Marino et al., 2001a, 2001b, 2001c). Additional research has emerged from this laboratory on EMF-induced animal and human brain activity changes that provides more evidence for the value of their research approach (Marino et al., 2002, 2003, 2004; Carrubba et al., 2006, 2007a, 2007b). *It is apparent that much remains to be examined and explained in EMF biological effects research through more creative methods of analysis than have been used before. The models described above need to be incorporated into risk assessment determinations.*

IV. Problems with Segregation of Effects by Artificial Frequency Bands that Ignore Modulation

One fundamental limitation of most reviews of EMF biological effects is that exposures are segregated by the physical (engineering/technical) concept of frequency bands favored by the engineering community. This is a default approach that follows the historical context established in the past by the incremental addition of newer technologies that generate increasingly higher frequencies. However, this approach fails to consider unique responses from biological systems that are widely reported at various combinations of frequencies, modulations and intensities.

When common biological responses are observed without regard for the particular, engineering-defined EMF frequency band in which the effects occur, this reorganization of the results can highlight the commonalities in biological responses caused by exposures to EMF across the different frequently bands. An attempt to introduce this concept to escape the limitations of the engineering-defined structure occurred with the development of the 1986 NCRP radiofrequency exposure guidelines because published papers from the early 1970s to the mid 1980s (to be discussed below) demonstrated the need to include amplitude modulation as a factor in setting of maximum exposure limits. The 1986 NCRP guideline was the one and only risk evaluation that included an exception for modulated fields.

The current situation argues strongly for a change in the way risk assessment is conducted, especially for the last 15 to 20 years. Unfortunately, subsequent risk evaluations did not follow the NCRP example, but returned to the former engineering-defined analysis conditions, in part because scientists who reported non-thermal effects were not placed on the review committees, and in the terms of Slovic (1999) "Risk assessment is inherently subjective and represent a blend of science and judgment with important psychological, social, cultural, and political factors. … Whoever controls the definition of risk controls the rational solution to the problem at hand. … Defining risk is thus an exercise in power." It appears that by excluding scientists experienced with producing non-thermal biological effects, the usually sound judgment by the selected committees was severely limited in its breadth-of-experience, thereby causing the members to retreat to their own limited areas of expertise when forced to make judgments, as described by Slovic (1999), "Public views are also influenced by worldviews, ideologies, and values; so are scientists' views, particularly when they are working at limits of their expertise." The current practice of segregating scientific investigations (and resulting public health limits) by artificial divisions of frequency dramatically dilutes the impact of the basic science results, thereby reducing and distorting the weight of evidence in any evaluation process (see evaluations of bias by Havas 2000, referring to NRC 1997 compared to NIEHS 1998 and NIEHS 1999).

A. Suggested Research

Are there substitute approaches that would improve on the health-effects evaluation situation? As mentioned above, it may be useful in certain cases to develop a biologically based clustering of the data to focus on and enrich understanding of certain aspects of biological responses. Some examples to consider for biological clustering include: 1) EMF features, such as frequency and intensity inter-dependencies, 2) common cofactors, such as the earth's magnetic field or co-incident application of chemical agents to perturb and perhaps sensitize the biological system to EMF, or 3) physiological state of the biological specimen, such as age or, sensitive sub-populations, including genetic predisposition (Fedrowitz et al., 2004, 2005).

To determine if this approach has merit, one could combine reports of biological effects found in the ELF (including sub-ELF) band with effects found in the RF band when the RF exposures are amplitude modulated (AM) using frequencies in the ELF band. The following data should be used: 1) human response time changes under ELF exposure (Hamer, 1968), 2) monkey response time and EEG changes under ELF exposure (Gavalas et al., 1970; Gavales-Medici & Day-Magdaleno, 1976), 3) cat brain EEG, GABA and calcium ion changes induced by ELF and AM-RF (Kaczmarek and Adey, 1973, 1974; Bawin et al. 1973), 4) calcium ion changes in chick brain tissue under ELF and AM-RF (Bawin et al., 1975, 1976, 1978a, 1978b; Sheppard et al., 1979; Joines and

Blackman et al., , 1981a, 1981b, 1986; Blackman et al., 1979, 1980a, 1980b, 1981, 1982, 1985, 1988a, 1988b, 1989, 1990), and 5) calcium changes under AM-RF in brain cells in culture (Dutta et al., 1984, 1989, 1992) and in frog heart under AM-RF (Schwartz et al., 1990). The potential usefulness of applying biological clustering in the example given above even though AM is used, is that the results may have relevance to assist in the examination of some of the effects reportedly caused by cellular phone exposures which include more complex types of modulation of RF. This suggestion is reasonable because three groups have recently reported human responses to cell phone emissions that include changes in reaction times (Preece et al., 1998, 1999; Koivisto et al. 2000a, 2000b; Krause et al., 2000a, 2000b) or to brain wave potentials that may be associated with reaction time changes (Freude et al., 1998, 2000).

The papers described above, published in the 1960s through 1991, foreshadowed the more recent publications in 1999 and 2000 showing response time changes, or associated measures, in human subjects during exposure to cell phone-generated radiation (although none of the earlier studies was acknowledged in these recent reports on cognition and reaction time). Without guidance from this extensive earlier work, the development of the mechanistic bases for non-thermal effects from EMF exposures will be substantially delayed.

V. Conclusions

• There is substantial scientific evidence that some modulated fields (pulsed or repeated signals) are bioactive, which increases the likelihood that they could have health impacts with chronic exposure even at very low exposure levels. Modulation signals may interfere with normal, non-linear biological processes.

• Modulation is a fundamental factor that should be taken into account in new public safety standards; at present it is not even a contributing factor.

• To properly evaluate the biological and health impacts of exposure to modulated RFR (carrier waves), it is also essential to study the impact of the modulating signal (lower frequency fields or ELF-modulated RF).

• Current standards have ignored modulation as a factor in human health impacts, and thus are inadequate in the protection of the public in terms of chronic exposure to some forms of ELF-modulated RF signals.

• The current IEEE and ICNIRP standards are not sufficiently protective of public health with respect to chronic exposure to modulated fields (particularly new technologies that are pulse-modulated and heavily used in cellular telephony).

• The collective papers on modulation appear to be omitted from consideration in the recent WHO and IEEE science reviews. This body of research has been ignored by current standard setting bodies that rely only on traditional energy-based (thermal) concepts.

• More research is needed to determine which modulation factors, and combinations are bioactive and deleterious at low intensities, and are likely to result in disease-related processes and/or health risks; however this should not delay preventative actions supporting public health and wellness.

• If signals need to be modulated in the development of new wireless technologies, for example, it makes sense to use what existing scientific information is available to avoid the most obviously deleterious exposure parameters and select others that may be less likely to interfere with normal biological processes in life.

• The current membership on Risk Assessment committees needs to be made more inclusive, by adding scientists experienced with producing non-thermal biological effects.

• The current practice of segregating scientific investigations (and resulting public health limits) by artificial divisions of frequency needs to be changed because this approach dramatically dilutes the impact of the basic science results and eliminates consideration of modulation signals, thereby reducing and distorting the weight of evidence in any evaluation process.

Disclaimer: the opinions expressed in this text are those of its author, and are not necessarily those of his employer.

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SECTION 15

EVIDENCE BASED ON EMF MEDICAL THERAPEUTICS

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July 2007

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I. Introduction

Electromagnetic fields are widely used in therapeutic medical applications. Proof of effectiveness has been demonstrated in numerous clinical applications of low-intensity ELF-EMF and RF-EMF, each treatment employing specific characteristics of frequency, modulation and intensity to achieve its efficacy. On the other hand, higher levels of EMFs encountered in the environment which are indiscriminately generated by technologies of the 20th and 21st centuries may result in harm. EMF levels which are allowable today under thermally-based public exposure standards do not take into account these clear indications of the sensitivities of the human body to EMFs. If we are to promulgate public exposure standards that are protective of public health, then this body of evidence on healing with EMFs is of primary importance in developing biologically-based public exposure standards.

"Although incompletely understood, tissue free radical interactions may extend to zero field levels. Emergent concepts of tissue thresholds to imposed and intrinsic magnetic fields address ensemble or domain functions of populations of cells, cooperatively whispering together in intercellular communication and organized hierarchically at atomic and molecular levels." 10

II. Therapeutic Uses for Electromagnetic Fields

Since EMFs have been shown to be effective in treating conditions of disease at energy levels far below current public exposure standards, this body of evidence forms a strong warning that indiscriminate EMF exposure is ill advised. Health concerns from indiscriminate exposure to EMF, as opposed to EMF exposures done with clinical oversight, could lead to harm as can the unsupervised use of pharmaceutical drugs.
The consequence of multiple sources of EMF exposure in daily life, with no regard to cumulative exposures or to potentially harmful combinations of EMF exposures will pose

future difficulties in identifying sources of disease (because of multiple and overlapping exposures) and time-varying and geography-varying differences from person to person. Just as ionizing radiation can be used to effectively diagnose disease and treat cancer, it is also a cause of cancer under different exposure conditions. Since EMFs are both a cause of disease, and also used for treatment of disease, it is vitally important that public exposure standards reflect our current understanding of the biological potency of EMF exposures.

"there is an abundance of experimental and clinical data demonstrating that exogenous EMFs of surprisingly low levels can have a profound effect on a large variety of biological systems. Both electrical and electromagnetic devices have been demonstrated to positively affect the healing process in fresh fractures, delayed and nonunions, osteotomies, and spine fusion in orthopedics and for chronic and acute wound repair. These clinical results have been validated by well-designed and statistically powered double-blind clinical trials and have survived meta-analyses. The FDA has approved labeling for these biophysical devices, limited at present to these indications." "The potential clinical applications of EMF therapeutics extend far beyond those considered here and the clinical rewards are certain to be huge." "Cancer, cardiac muscle regeneration, diabetes, arthritis, and neurological disorders are just some of the pathologies that have already been shown to be responsive to EMF therapy. Successful applications of low-frequency EMFs have been reported for treatment of bronchial asthma, myocardial infarction, and venous and varicose ulcers. There is emerging research on EMF effects on angiogenesis and the manner in which this may increase stem cell survival in the treatment of Altzeimer's (sic) and Parkinson's diseases. There are also many studies that point to the possibility of the use of EMF for peripheral nerve regeneration" and *" the treatment of cancer." "EMF therapy modalities are simple, safe and significantly less costly to the health care system. They offer the ability to treat the underlying pathology rather than simply the symptoms. The time is particularly opportune given the increased incidence of side effects from the use of pharmacological agents. EMF therapeutics will have a profound impact upon health and wellness and their costs worldwide."* [1]

A. Bone Repair

Clinical use of pulsed EMF has been demonstrated to achieve bone repair, particularly in fractures that do not heal on their own. Bone healing is stimulated by very weak electromagnetic fields that are far lower in strength than would produce tissue heating. The FDA approved pulsed EMF for use in bone healing in 1979. Since that time, many millions of patients have benefited from this therapy. Since PEMF treatments are non-invasive and clinically effective, it has advantages to the patient in terms of reduced pain and suffering, reduction in health care costs, and effectiveness where other methods have failed to produce adequate clinical results.

"It is now commonplace to learn the successful use of weak, nonthermal electromagnetic fields (EMF) in the quest to heal, or relieve the symptoms of a variety of debilitating ailments. This chapter attempts to give the reader an introduction and assessment of EMF modalities that have demonstrated therapeutic benefit for bone and wound repair and chronic and acute pain." [2]

Pilla provides extensive discussion of the "clinical evidence that time-varying magnetic fields (EMF) can modulate molecular, cellular and tissue functions in a physiologically significant manner." [2] A description of the various waveforms and EMF modalities which are effective in bone and wound repair are beyond the scope of this paper, but are well documented. [2] In addition to documenting that bone repair in fractures is achieved with pulsed EMF at low intensities, Pilla also reports that pulsed EMF has been successful in promoting bone repair and healing of spine fusions for the treatment of chronic back pain from worn and/or damaged spinal discs. [3] The FDA has approved pulsed EMFs for bone healing and this is a widely recognized treatment, particularly for fractures that are slow to heal, or do not repair with conventional medical treatment. It represents one of the best documented cases in science where the body clearly responds to low-intensity EMF signals for healing purposes; these EMF signals are far below current public exposure standards and are proof of the bioactivity (in a beneficial form as applied).

Liboff describes signal shapes in electromagnetic therapies that contribute greatly to our understanding of the various forms of EMF signal delivery that are fundamental to eliciting specific bioeffects. He simply and elegantly describes electric and magnetic signal characteristics, their signature shapes and methods of delivery (time-varying, oscillatory, or modulated) which create special interactions with human tissues and organs for healing. [4]

"It is likely that the future will see combinations of such signals in therapeutic applications, especially as more information filters back from the laboratory elaborating on the nature of electromagnetic interactions with living tissue." [4]

B. Wound Repair

The clinical application of pulsed EMF has been shown to enhance wound repair and healing. [2,5] Devices that use pulsed EMF have been approved for use in the United States by the FDA. Pilla reports "*the clear clinical effectiveness of PEMF signals has resulted in significantly increased use*" in treating wounds that do not heal. [5] In Pilla's extensive summary presented on beneficial effects of EMF on wound healing, he reports pulsed EMF has been reported to reduce edema, increase blood flow, modulate upregulated growth factor receptors, enhance neutrophil and macrophage attraction and epidermal cell migration, and increase fibroblast and granulation tissue proliferation. Most wound studies were conducted on arterial or venous skin ulcers, diabetic ulcers, pressure ulcers, and surgical and burn wounds. [5] Wound repair under the influence of very low level pulsed EMFs is a second solid documentation in science that very low level EMFs are bioactive (in this case, beneficial) when applied in very specific clinical applications where the exposure variables are carefully selected.

Oschman provides an overview of the evolution of energy medicine and electromagnetic energy treatments related to bone repair, wound healing, pain relief, depression, insomnia, inflammation of tissues and other medical conditions. [6] He also underscores the counter-intuitive thesis that low-intensity EMFs can be more effective in eliciting healing responses than larger intensity exposures; and that understanding of the subtle energies and their specific interactions with human functioning is imperative.

(l)iving tissues are far more sensitive to external fields than previously realized. After a period when physicists were certain that observed sensitivities to nonionizing and nonthermal radiations wer physically impossible, we now know that biological systems defy the simple logic that larger stimuli should produce larger responses.For many living systems, extremely weak fields can be more effective than strong fields." [6]

C. Pain Management

Pulsed magnetic field (PMF) devices are also used with FDA approval for *"relief of acute and chronic pain and the reduction of edema* (swelling*), all symptoms of wounds from post-surgical procedures, musculoskeletal injuries, muscle and joint overuse, as well as for chronic wounds."* [5]

Pulsed EMF has been shown to be effective in relief of chronic pain associated with connective tissue injury (cartilage, tendon, ligaments and bone) and soft-tissue injuries associated with the joints. Both acute and chronic pain may be successfully treated with EMFs as an alternative to non-steroidal anti-inflammatory drugs (NSAIDs). Relief from chronic pain due to osteoarthritis has been reported with treatment by EMFs. [2]

Markov reports that EMF is used in treatment of pain associated with tendonitis, multiple sclerosis, carpal tunnel syndrome and some forms of arthritis. He discusses the use of pulsed EMF for headache and migraine pain relief; neck and whiplash injuries, postoperative pain, sprains, chronic pelvic pain, and nerve regeneration. Pain reduction by clinical application of pulsed EMF is achieved with non-thermal levels of exposure, and produces a nonthermal biological effect. [8]

D. Depression, Anxiety Disorders, Insomnia

"Today (2002) we are at a threshold for the acceptance of electromagnetic therapy as a clinically accepted form of therapy for such diverse diseases as unipolar depression, Parkinson's disease, and sleep disorders and the treatment of debilitating chronic and acute pain." [8]

Shealy et al (2007) detail clinical findings for treatment of depression and mood management, reduction in anxiety, and treatment of insomnia. 10 Electrical energy stimulators that deliver very low-level EMF have been reported to be clinically effective in the alteration of neurobioechemicals including serotonin and cortisol. Depression, mood disorders and insomnia have been related to disregulation of serotonin levels. Use of EMFs to reduce symptoms of depression, anxiety and insomnia are authorized by the FDA, and have been in use since the 1970's. Shealy reports that transcranial stimulation by EMFs led to a significant relief of depression in 85% of patients who had failed pharmacological agents, and was at least twice as effective as any known antidepressant drugs and without complications. [10]

E. Protection from Anoxia (Protection for the Heart)

The work of Albertini, Litovitz and di Carlo, Goodman and Blank, Han, Pipkin, Rasmark and Kwee, [11-17] has shown that very weak ELF-EMF and RF-EMF exposures can actually help to protect cells against tissue damage. They can induce an adaptive stress response in cells, which in turn helps the cell fight damage. The response is production of stress proteins (heat shock proteins or HSP). These stress proteins help to protect the cells against injury and death. A 20-minute exposure to electromagnetic fields at only 80 mG will start stress protein production, which helps to fight cellular damage from lack of oxygen, for example. Protection from anoxia (or lack of oxygen) is important in heart attacks. Pre-treatment with ELF-EMF (and also RF-ELF) before blocking oxygen to cells has been shown to be protective against the lack of oxygen to heart tissues. The exposure level is on the order of 80 mG ELF-EMF or far below any possible thermal heating.

This means that there are clinical applications for protection against heart attack damage that can be provided by very low-dose EMF exposures. Such protection could be vitally important in reducing damage from oxygen loss during heart attacks. It is another line of proof that low-intensity electromagnetic fields are bioactive, and when applied in specific therapeutic ways, are beneficial. It also underscores that the body can detect and decode these very weak signals, providing further evidence that thermally-based standards are incomplete because they do not take into account the sensitivity of the human body to non-thermal levels of EMF exposure.

IV. Conclusions

Since EMFs have been shown to be effective in treating conditions of disease at energy levels far below current public exposure standards, this body of evidence forms a strong warning that indiscriminate EMF exposure is ill advised.

Based on extensive clinical applications of low-intensity EMFs since at least the 1970s, it has been demonstrated beyond argument that some forms of EMFs can be medically effective in treating a wide variety of human health disorders and injuries. Since all of these treatments are conducted at energy levels that do not involve tissue heating per se, it is convincing proof that the human body both reacts to and can be affected by exposures to EMFs. Exposures can be beneficial when EMFs are applied with conscious knowledge of the exposure factors that are proven to lead to specific biological (healing) consequences. The intensity of such therapeutic exposures nearly always falls below current public exposure standards as discussed in Section 3.

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SECTION 16

"Late Lessons From Early Warnings:

Towards realism and precaution with EMF?"

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Disclaimer.

The views expressed are those of the author and do not represent the views of the EEA or its Management Board. The author has no competing financial interest in the matters dealt with.

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I. INTRODUCTION

The histories of selected public and environmental hazards, from the first scientifically based early warnings about potential harm, to the subsequent precautionary and preventive measures, have been reviewed by the European Environment Agency.(“Late Lessons from Early Warnings: the Precautionary Principle 1896-2000”, EEA,2001). This paper summarises some of the definitional and interpretative issues that arise from the report and subsequent debates, such as the contingent nature of knowledge; the definitions of precaution, prevention, risk, uncertainty, and ignorance; the use of differential levels of proof; and the nature and main direction of the methodological and cultural biases within the environmental health sciences. These issues are relevant to EMF.

II. THE TWELVE “LATE LESSONS FROM EARLY WARNINGS

The paper does not address the specifics of EMF hazards, leaving it to the reader to apply, or not, the “Twelve late Lessons” that conclude the report. These lessons attempt to synthesise the fourteen historical experiences from the very different case study chapters into generic knowledge that can help inform policy-making on current issues such as GMO,, nanotechnologies, mobile phones, and endocrine disrupting substances where the luxuries of hindsight are not yet available but where exposures are already widespread and rising.

The idea of the twelve late lessons is to make the most of past experience to help anticipate future surprises whilst recognising that history never exactly repeats itself. When adopted alongside the best available science the lessons aim to help minimize hazards without compromising innovation. The “lessons” are reproduced below.

A. “Identify/Clarify the Framing and Assumptions”

1. Manage “risk”, “uncertainty” and “ignorance”
2. Identify/reduce “blind spots” in the science
3. Assess/account for all pros and cons of action/inaction
4. Analyse/evaluate alternative options

5. Take account of stakeholder values
6. Avoid “paralysis by analysis” by acting to reduce hazards via the precautionary principle.

B. “Broaden Assessment Information”

7. Identify/reduce interdisciplinary obstacles to learning
8. Identify/reduce institutional obstacles to learning
9. Use “lay”, local as well as specialist knowledge
10. Identify/anticipate “real world” conditions
11. Ensure regulatory and informational independence
12. Use more long-term (ie. decades) monitoring and research

III. EARLY USE OF PRECAUTION

The Vorsorgeprinzip, or “foresight” principle, only emerged as a specific policy tool during the German debates on the possible role of air pollution as a cause of “forest death” in the 1970-80s. However, John Graham, one of Bush’s science policy advisors, and trenchant critic of the precautionary principle, has noted that:

> *“Precaution, whether or not described as a formal principle, has served mankind well in the past and the history of public health instructs us to keep the spirit of precaution alive and well”*. (Graham 2002).

Graham might have been thinking of the cholera episode of 1854 when precaution did indeed serve the people of London well. Dr. John Snow, a London physician, used the spirit of precaution to advise banning access to the polluted water of the Broad St. pump which he suspected was the cause of the cholera outbreak. He based his recommendation on the evidence he had been accumulating for some years including his study of S. London populations served by both piped and well water. Snow’s views on cholera causation were not shared by The Royal College of Physicians who considered Snow’s thesis and rejected it as ‘untenable’ as they and other “authorities” of the day believed that cholera was caused by airborne contamination. This particular scientific “certainty” soon turned out to be certainly mistaken, with the last remaining doubt being removed when Koch in Germany isolated the cholera vibrio in 1883.

From the *association* between exposure to water polluted with human faeces, and cholera, observed by Snow in 1854, to Koch's discovery of the *"mechanism of action"*, took 30 years of further scientific inquiry. Such a long time lag between acknowledging compelling associations and understanding their mechanisms of action is a common feature of scientific inquiry, as the histories of TBT, PCBs, DES, the Great Lakes pollution, beef hormones and the other cases in the EEA report illustrate.

IV. KNOWLEDGE AND IGNORANCE REQUIRES BOTH PREVENTION AND PRECAUTION

The Broad St. pump, TBT, DES, PCBs and Great Lakes Pollution examples described here also serve to illustrate the contingent nature of knowledge. Today's scientific certainties can be tomorrow's mistakes, and today's research can both reduce and increase scientific uncertainties, as the boundaries of the "known" and the unknown expand. Waiting for the results of more research before taking action to reduce threatening exposures may not only take decades but the new knowledge may identify previously unknown sources of both uncertainty and ignorance, as awareness of what we do not know expands, thereby supplying further reasons for inaction. "Paralysis by Analysis " can then follow.

"The more we know, the more we realise what we don't know" is not an uncommon scientific experience. Socrates observed some time ago:
"I am the wisest man alive, for I know one thing, and that is that I know nothing".
(Plato's Apology 1.21).

This was an early lesson in humility that has been lately forgotten by many scientists and politicians, who often put what turns out to be "misplaced certainty" in today's scientific knowledge: or assume that uncertainty can only be reduced, and not increased, by further research.

The distinction between uncertainty and ignorance is important. (Stirling, 1999) Ignorance is knowing that today's knowledge is very limited: it is the source of scientific surprises, such as the hole in the ozone layer, the mesothelioma cancer from asbestos, imposex in sea snails etc. It is distinct from the uncertainties that arise from gaps in knowledge and from variances in sampling and monitoring; parameter variability; model assumptions; and from the other attempts to approximate, model and predict unfolding realities.

Foreseeing and preventing hazards in the context of ignorance presents particular challenges to decision-makers. At first sight it looks impossible to do anything to avoid or mitigate “surprises”. And ignorance ensures that there will always be surprises. However, some measures that could help limit the consequences of ignorance and the impacts of surprises are:

- using intrinsic properties as generic predictors for unknown but possible impacts e.g. the persistence, bioaccumulation and spatial range potential of chemical substances. (Stroebe et al., 2004)
- reducing specific exposures to potentially harmful agents on the basis of credible ‘early warnings’ of *initial* harmful impacts, thus limiting the size of any other ‘surprise’ impacts from the same agent, such as the asbestos cancers that followed asbestosis; and the PCB neurotoxicological effects that followed its wildlife impacts.
- promoting a diversity of robust and adaptable technological and social options to meet needs, which limits technological ‘monopolies’ (such as those like asbestos, CFCs, PCBs etc.), and therefore reduces the scale of any ‘surprise’ from any one technological option.
- using more long-term research and monitoring of what appear to be “surprise sensitive sentinels”, such as frogs and foetuses.

A. Prevention and Precaution

The distinction between *prevention* and *precaution* is also important. Preventing hazards from “known” risks is relatively easy and does not require precaution. Banning smoking, or asbestos, today requires only acts of prevention to avoid the well-known risks. However, it would have needed precaution, (or foresight, based on a sufficiency of evidence), to have justified acts to avoid exposure to the then uncertain hazards of asbestos in the 1930s –50s, or of tobacco smoke in the 1960’s). Such precautionary acts then, if implemented successfully, would have saved many more lives in Europe than today’s bans on asbestos and smoking are doing. As

Cogliano has recently pointed out, the difference between prevention and precaution can be further illustrated by showing that *prevention* is used to justify the restriction of exposure to an IARC Category 1 carcinogen whereas *precaution* is necessary to justify restricting exposure to a Category 2A or B carcinogen, where the evidence is less strong. The section below. on different levels of proof , further elaborates this point.

For EMF, the question is, does the existing strength of evidence justify *precautionary* actions now? Or will exposure reduction be delayed until the evidence is clear enough to justify the more belated and overall less protective *prevention* of "known" causes, so that EMF replicates the fate of asbestos ,smoking and most of the other cases in the EEA report?

Some commentators, who have a long and distinguished history in preventing occupational and environmental risks, have queried the added value of the precautionary principle in the field of public health, with its long traditions of prevention. (Goldstein, 2007).

The key to understanding the added value of the PP requires a) acknowledging the distinction between prevention and precaution described above; b) an appreciation of the further distinctions between the primary, secondary and tertiary preventative *measures* that have long between adopted in public health, and the prior *justification* for any such measure, which the PP brings; and c) a recognition of the increased legitimacy and transparency that arises from the articulation and adoption of the PP in legal texts, international agreements and conventions, as opposed to being merely part of general practice.

More empirically, the evidence that many scientific disciples, legal scholars (de Sadeleer, 2007),and international policymakers, have, since the 1970s, recognised the need for legitimising the PP as a new policy tool that is better able to deal with systems complexities, ignorance and uncertainties, suggests that the PP brings added value to the protection of the environment and the public.

There is much discussion generated by the different meanings often attached to the common terms “prevention”, “precaution”, “risk”, “uncertainty” and “ignorance”. **Table 1** attempts to clarify these so as to help reduce unnecessary argumentation.

Table 1: Clarification of Key Terms

Situation	***State and dates of knowledge***	***“Nature of the justification for Action”***
Risk	**‘Known’ impacts; ‘known’ probabilities e.g. asbestos**	**Prevention: action taken to reduce known hazards e.g. eliminate exposure to asbestos dust**
Uncertainty	**‘Known’ impacts; ‘unknown’ probabilities e.g. antibiotics in animal feed and associated human resistance to those antibiotics**	**Precautionary prevention: action taken to reduce exposure to potential hazards**
Ignorance	**‘Unknown’ impacts and therefore ‘unknown’ probabilities eg the ‘surprises’ of chlorofluorocarbons (CFCs) pre 1974**	**Precaution: action taken to anticipate, identify and reduce the impact of ‘surprises’**

Source: Reproduced, with amendment, from the Late Lessons Report, EEA 2001.

V. THE PRECAUTIONARY PRINCIPLE: DEFINITIONS AND INTERRPRETATIONS

There are some relatively rare but successful acts of “precautionary prevention” in the EEA report such as on cholera in1854, on TBT in France in the 1980s, and on CFCs in the 1970s. Together with the many other examples of the failure to use the precautionary principle in the other case studies (EEA, 2001), these illustrate the wisdom of taking appropriate precautionary actions to avoid plausible and serious threats to health or environments, especially when the impacts are irreversible and likely to be much more costly to society than the precautionary measures.

Some commentators have stressed the need for policymakers to take account of the foreseeable, or plausible, countervailing (secondary) costs of otherwise genuine precautionary attempts to protect the environment and health. (Rushton, 2007). This consideration of countervailing costs has long been recognised by the better policymakers, even if it is difficult in practice to anticipate and account for all consequences of actions. And of course there are the secondary benefits of precautionary actions as well, which tend to be less stressed, such as the benefit of reduced respiratory and cardiovascular disease from the reduced combustion of fossil fuels: a large and early secondary benefit of that climate change measure.

The outcomes of some controversial actions based on the PP, such as the EU ban on antibiotics as growth promoters, which is a Late Lessons case study, have since been scrutinised, and have been considered sound ,or unsound, depending on the science used and its interpretation by different interests. (Cox, 2007, Angulo et al., 2004).

Any policy effectiveness analysis of measures taken to deal with such multi-causal and long term hazards as antibiotics as growth promoters is fraught with methodological difficulties and is hampered by long latencies and complex biological systems: untangling the causal impact of one stressor amongst many inter-dependent ones is virtually impossible. The value of applying more probabilistic and value of information data to such conundrums is recognised by many risk managers. However, this cannot remove the need for scientific and political judgment about how to take appropriate and proportionate action in the face of irreducible uncertainties, ignorance and plausible hazards which could have serious, widespread and irreversible impacts and for which probabilities are not possible at the time when they are most needed. This is the current case with many EMF exposures.

A. Some Definitions and Interpretations of the Precautionary Principle

The increasing awareness of complexity and uncertainty during the 1980/90's led to the German debates on the Vorsorgeprinzip shifting to the international level, initially in the field of conservation (World Charter for Nature UN 1982), but then particularly in marine pollution, where an overload of data accompanied an insufficiency of knowledge. (Marine Pollution Bulletin, 1997). This generated the need to act with precaution to reduce the large amounts of chemical pollution entering the North Sea. Since then many international treaties have included the PP (including the often cited version from the Third North Sea Ministerial Conference, 1990, have included reference to the precautionary principle, or, as they refer to it in the USA, the precautionary approach.

The N.Sea declaration called for *"action to avoid potentially damaging impacts of substances, even where there is no scientific evidence to prove a causal link between emissions and effects"*.

This definition has often, and sometimes mischievously, been used to deride the precautionary principle by claims that it appears to justify action even when there is "no scientific evidence" that associates exposures with effects. However, the N. Sea Conference definition clearly links the words "no scientific evidence" with the words. "to prove a causal link". We have already seen with the Broad St. pump and TBT examples that there is a significant difference between evidence about an "association" and evidence that is robust enough to establish a "causal" link. (Hill, 1965).

The Treaty of the European Union also cites the precautionary principle, as well as the other key principles of sound public policy on health:

> "*Community policy on the environment … shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should, as a priority, be rectified at the source and the polluter should pay*" (Treaty on European Union, 1992).

Other parts of the EU Treaty ,and cases taken at the European Court of Justice, make it clear that these principles also apply to environmental and consumer protection issues.

These principles, as well as the important and legally required *proportionality principle,* which limits disproportion between the costs and benefits of prevention, are not defined in the Treaty but are illuminated by their practical application in case law. However, all serious applications of the precautionary principle require some scientific evidence of a plausible association between exposures and current, or potential, impacts.

There is still much disagreement and discussion about the interpretation and practical application of the precautionary principle, due, in part, to this lack of clarity and consistency over its definition. For example, many definitions in the Treaties and Conventions use a double negative to define the precautionary principle: that is, they identify reasons that cannot be used to justify not acting, but without specifying that a sufficiency of evidence is needed to justify taking action.

B. Reasonable Grounds for Concern?

The Communication from the EU on the precautionary principle (European Commission 2000) does specify that "reasonable grounds for concern" are needed to justify action under the precautionary principle, but it does not make explicit that these grounds will be case specific: nor does it explicitly distinguish between risk, uncertainty and ignorance. Since the EC Communication, the EU Council of Misisters, EU case law, and the regulation establishing the new European Food Safety Authority, EFSA, (General Food Law Regulation, EC No 178/2002), have further clarified the circumstances of use and application of the precautionary principle.
For example, the judgement of the European Court of Justice in the BSE case contained a general definition which authoritative commentators think contain many of the necessary elements of the precautionary principle that are applicable in all areas of the EC law:

> "*Where there is uncertainty as to the existence or extent of risks to human health, the institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent*" (Christoforou, 2002).

The WHO Declaration from the Fourth Ministerial Conference on Environment and Health (WHO, 2004a) refers explicitly to the precautionary principle with the recommendation:

> *"that it should be applied where the possibility of serious or irreversible damage to health or the environment has been identified and where scientific evaluation, based on available data, proves inconclusive for assessing the existence of risk and its level but is deemed to be sufficient to warrant passing from inactivity to policy alternatives"* (WHO, 2004b).

The American Public Health Association (APHA) affirmed endorsement of the precautionary principle as a cornerstone of public health for the protection of children's health. In a 2000 policy statement, the APHA encouraged governments, the private sector and health professionals to promote and use the precautionary principle to protect the health of developing children (APHA, 2001).

C. The EEA working definition of the Precautionary Principle.

The working definition used in the European Environment Agency that has been developed during debates since 2001 is explicit about specifying both uncertainty and ignorance, as contexts for applying the principle, and in acknowledging that a case-specific sufficiency of scientific evidence is needed to justify public policy actions:

> '*The Precautionary Principle provides justification for public policy actions in situations of scientific complexity, uncertainty and ignorance, where there may be a need to act in order to avoid, or reduce, potentially serious or irreversible threats to health or the environment, using an appropriate level of scientific evidence, and taking into account the likely pros and cons of action and inaction*' (Gee, 2006).

The definition is also explicit about the trade off between action and inaction, and widens the conventionally narrow, and usually quantifiable, interpretation of costs and benefits to embrace the wider and sometimes unquantifiable, "pros and cons". Some of these wider issues, such as loss of the ozone layer, or of public trust in science, are unquantifiable, but they can sometimes be more damaging to society than the quantifiable impacts: and they need to be included in any comprehensive risk assessment. The EEA definition is proving to be useful in clarifying the use and interpretation of the PP, especially in emerging issues such as EMF.

VI. DIFFERENT LEVELS OF PROOF FOR DIFFERENT PURPOSES

The level of proof (or strength of scientific evidence) that would be appropriate to justify public action in each case varies with the pros and cons of action or inaction. These include the nature and distribution of potential harm; the justification for, and the benefits of the agent or activity under suspicion; the availability of feasible alternatives; and the overall goals of public policy. Such policy goals can include the achievement of the "high levels of protection" of public health, of consumer safety, and of the environment, required by the EU Treaty.

The use of different levels of proof is not a new idea: societies often use different levels of proof like for different purposes.

For example, a high level of proof (or strength of evidence) such as “beyond all reasonable doubt” is used to achieve good science where A is seen to cause B only when the evidence is very strong. Such a high level of proof is also used to minimise the costs of being wrong in the criminal trial of a suspected murderer, where it is usually regarded as better to let several guilty men go free than it is to wrongly convict an innocent man. However, in a different, civil trial setting, where, say, a citizen seeks compensation for neglectful treatment at work, which has resulted in an accident or ill health, the court often uses a lower level of proof commensurate with the costs of being wrong in this different situation. I n compensation cases an already injured party is usually given the benefit of the doubt by the use of a medium level of proof, such as “balance of evidence or probability”. It is seen as being less damaging (or less costly in the wider sense) to give compensation to someone who was *not* treated negligently than it is to *not* provide compensation to someone who was treated negligently. The “broad shoulders” of insurance companies are seen as able to bear the costs of mistaken judgements rather better than the much narrower shoulders of an injured citizen. In each of these two illustrations it is the nature and distribution of the costs of being wrong that determines the level of proof (or strength of evidence) that is “appropriate” to the particular case.

Bradford Hill, cited above, was very concerned about the social responsibility of scientists and he concluded his classic 1965 paper on association and causation in environmental health , which was prepared at the height of the smoking controversy, with a “call for action” in which, *inter alia*, he also proposed the concept of case specific and differential levels of proof. His three examples ranged from “relatively slight” to “very strong” evidence, depending on the nature of the potential impacts and of the pros and cons in each specific case, i.e., possibly teratogenic medicine for pregnant women; a probable carcinogen in the workplace; and government restrictions on public smoking or diets. (Bradford Hill 1965).

Identifying an appropriate level of proof has also been an important issue in the climate change debates. The International Panel on Climate Change (IPCC) discussed at length this issue before formulating their 1995 conclusion that "on the balance of evidence" mankind is disturbing the global climate. They further elaborated on this issue in their 2001 report where they identified 7 levels of proof (or strengths of evidence) that can be used to characterise the scientific evidence for a particular climate change hypothesis.

Table 2 provides the middle 5 of these levels of proof from the IPPC and illustrates their practical application to a variety of different societal purposes. In the cancer field the International Agency for Research on Cancer also uses several strengths of evidence to characterise the scientific evidence on carcinogens. (Cogliano, 2007)

Different Levels of Proof for Different Purposes: Some Examples and Illustrations

Probability	Quantitative descriptor (Probability bands based on IPCC 2001)	Qualitative Descriptor	Illustrations
100 % probability	Very likely (90-99 %)	• “Statistical significance”	• Part of strong scientific evidence for “causation”
		• “Beyond all reasonable doubt”	• Most criminal law. And the Swedish Chemical law, 1973, for evidence of ”safety” of substances under suspicion- burden of proof on manufacturers
90 %	Likely (66-90 %)	• “Reasonable certainty”	• Food Quality Protection Act, 1996 (US)
		• “Sufficient scientific evidence”	• To justify a trade restriction designed to protect human, animal or plant health under World Trade Organisation Sanitary and Phytosanitary (SPS) Agreement, Art. 2.2, 1995
50 %	Medium Likelihood (33-66 %)	• ”Balance of evidence”	• Intergovernmental Panel on Climate Change 1995 & 2001
		• ”Balance of probabilities”	• Much Civil and some administrative law
		• ”Reasonable grounds for concern ”	• European Commission Communication on the Precautionary Principle 2000
		• ”Strong possibility ”	• British Nuclear Fuels occupational radiation compensation scheme, 1984 (20-50% probabilities triggering different awards up to 50% +, which then triggers full compensation)
	Low Likelihood (10-33 %)	• ”Scientific suspicion of risk ”	• Swedish Chemical law, 1973, for sufficient evidence to take precautionary action on potential harm from substances-burden of proof on regulators
0 %		• ”Available pertinent information ”	• To justify a provisional trade restriction under WTO SPS Agreement, Art. 5.7 where ”scientific information is insuffiicient ”
	Very Unlikely (1-10 %)	• Low risk	• Household fire insurance
0 % probability		• ”Negligible and insignificant ”	• Food Quality Protection Act, 1996 (US)

Source: EEA, 2001

VII. FALSE NEGATIVES AND FALSE POSITIVES.

All of the 14 case studies (tributylin or TBT, benzene, PCBs, CFCs, MTBE, SO_2. Great Lakes pollution. DES, and beef hormones. asbestos. medical x-rays, BSE and Fisheries are all examples of “false negatives” in the sense that the agents or activities were regarded as not harmful for some time before evidence showed that they were indeed hazardous.

We tried to include a “false positive” case study in the report (i.e., where actions to reduce potential hazards turned out to be unnecessary), but failed to find either authors or sufficiently robust examples to use. Providing evidence of “false positives” is more difficult than with “false negatives” (Mazur, 2004). How robust, and over what periods of time, does the evidence on the absence of harm have to be before concluding that a restricted substance or activity is without significant risk?

Volume 2 of “Late Lessons”, which the EEA intends to publish in 2008, will explore the issues raised by false positives. including lessons to be learned from such apparent examples as the EU ban on food irradiation and hazardous labelling on saccharin in the US. The Y2K computer bug story may also carry some interesting lessons.

Why are there so many “false negatives” to write about, and how might this be relevant to EMF? Conclusions based on the first Late lessons volume of case studies point to two main answers: the bias within the health and environmental sciences towards avoiding “false positives”, thereby generating more “false negatives”, and the dominance within decision-making of short-term, specific, economic and political interests over the longer term, diffuse, and overall welfare interests of society.

The latter point needs to be further explored, particularly within the political sciences. Researchers could examine the ways in which society’s long-term interests can be more effectively located within political and institutional arrangements that have, or could have, an explicit mandate to look after the longer term welfare of society, and thereby to better resist the short-term pressures of particular economic or political interests. The judiciary in democracies can play part of this role, as can long running and independent advisory bodies, such as the Royal Commission on Environmental Pollution (UK), or the German Advisory Council on Global Change.

The current and increasing dominance of the short-term in markets and in parliamentary democracies makes this an important issue. The experiments we are conducting with planet earth, its eco-systems and the health of its species, including humans, require, *inter alia*, more long-term monitoring of "surprise-sensitive" parameters which could, hopefully, give us early warnings of impending harm. Such long-term monitoring requires long-term funding, via appropriately designed institutions: such funding and institutions are in short supply. The case studies in Vol. 1 of "Late Lessons" illustrate both the great value, (e.g. in the TBT, DES, Great Lakes and CFCs stories), yet relative paucity, of long-term monitoring of both health and environments. Such monitoring can contribute to the "patient science" that slowly evolving natural systems require for their better understanding.

Since the publication of "Late Lessons" we have further explored the second cause of "false negatives" i.e. the issue of bias within the health and environmental sciences. Table 3 lists sixteen common features of methods and culture in the environmental and health sciences and shows their main directions of error. Of these, only three features tend towards generating "false positives" whereas twelve tend towards generating "false negatives". (Clearly, the weighting of these different biases would be the next step but has not yet been tried).

Table 3

ON BEING WRONG:
Environmental and Health Sciences and Their Directions of Error

SCIENTIFIC STUDIES	SOME METHODOLOGICAL FEATURES	MAIN[1] DIRECTIONS OF ERROR-INCREASES CHANCES OF DETECTING A:
Experimental	• High doses	• False positive
Studies	• Short (in biological terms) range of doses	• False negative
(Animal	• Low genetic variability	• False negative
Laboratory)	• Few exposures to mixtures	• False negative
	• Few Foetal-lifetime exposures	• False negative
	• High fertility strains	• False negative (Developmental/reproductive endpoints)
Observational	• Confounders	• False positive
Studies	• Inappropriate controls	• False positive/negative
(Wildlife &	• Non-differential exposure misclassification	• False negative
Humans)	• Inadequate follow-up	• False negative
	• Lost cases	• False negative
	• Simple models that do not reflect complexity	• False negative
Both	• Publication bias towards positives	• False positive
Experimental And	• Scientific cultural pressure to avoid false positives	• False negative
Observational Studies	• Low statistical power (e.g. From small studies)	• False negative
	• Use of 5 % probability level to minimise chances of false positives	• False negative

Source: Gee, 2006

[1] Some features can go either way (e.g. inappropriate controls) but most of the features mainly err in the direction shown in the table

The general bias towards the null helps to produce robust science, basing it on strong foundations of knowledge, but this bias can encourage poor public health or environmental policy. The goals of science and public policy-making on health and environmental hazards are different: science puts a greater priority on avoiding “false positives” by accepting only very high levels of proof of “causality”, whereas public policy tries to prioritize the avoidance of “false negatives” on the basis of a sufficiency of evidence of potential harm.

Table 3 is derived from papers presented to a conference on the precautionary principle organised by the Collegium Ramazzini, the EEA, the WHO and NIEHS in 2002. (Grandjean et al., 2003). It provides a first and tentative step in trying to capture and communicate the main directions of this bias within the environmental and health sciences, a bias which decision makers and the public should be aware of. As they debate the evidence on emerging hazards such as EMF.

The appropriate balance between false negatives and positives was addressed at a JRC/EEA workshop on the precautionary principle and scientific uncertainty which was held during the “Bridging the Gap” Conference, 2001, organised by the Swedish Presidency of the EU, in partnership with the EEA and DG Research. It drew the following conclusion:

> *“Improved scientific methods to achieve a more ethically acceptable and economically efficient balance between the generation of “false negatives” and “false positives” are needed”*. (Swedish EPA 2001).

VIII. SOME CRITERIA FOR ESTABLISHING CAUSATION

Bradford Hill established nine criteria for helping to move from association to causation in environmental health which have been, and still are, widely used in debates on issues such as EMF

Two of the apparently more robust of the “criteria” may not be so robust in the context of multi-causality, complexity and gene/host variability.

For example, ***“consistency”*** of study findings is not always to be expected. As Prof. Needleman, who provided the first of what could be called the second generation of early warnings on lead in petrol in 1979 has observed:

> *"Consistency in nature does not require that all or even a majority of studies find the same effect. If all studies of lead showed the same relationship between variables, one would be startled, perhaps justifiably suspicious"* (Needlemann , 1995).

It follows that the *presence* of consistency of results between studies on the same hazard can provide robust evidence for a causal link, but the *absence* of such consistency may not provide very robust evidence for the absence of a real association. In other words, the "criterion" of consistency is asymmetrical, like most of the other Bradford Hill "criteria".

Similarly, the criterion of ***"temporality",*** which says that the putative cause X of harm Y must come before Y appears, is robust in a simple, uni-causal world. In a multi-causal, complex world of common biological end points that have several chains of causation this may not necessarily be so. For example, falling sperm counts can have multiple, co-causal factors, some of which may have been effective at increasing the incidence of the biological end point in question in advance of the stressors in focus, thereby confusing the analysis of temporality. The resulting overall sperm count trends could then be rising, falling or static, depending on the combined direction and strengths of the co-causal factors and the time lags of their impacts. It follows that say, chlorine chemicals, may or may not be co-causal factors in falling sperm counts: but the use of the "temporality" argument by the WHO, who observed that sperm counts began to fall before chlorine chemistry production took off, does not provide robust evidence that they are not causally involved.

The presence of "temporality", like "consistency" may be robust evidence *for* an association being causal, but its *absence* may not provide robust evidence *against* an association. Bradford Hill was explicitly aware of the asymmetrical nature of his "criteria": his followers have not always been so aware.
During 2005, the 40th anniversary year of the Bradford Hill "criteria", the EEA convened a panel of experts to review the "criteria" and their use in light of advances in knowledge, particularly multi-causality, since 1965. A report will be published in 2007.

How this goal can be achieved without compromising science remains to be explored, (Grandjean 2004; Grandjean et al., 2004). It is clearly necessary, particularly when dealing with EMF, for scientific methods to not only take account of thisfalse negative/positive bias in methodologies but also to more clearly reflect other realities such as multi-causality; thresholds; timing of dose; sensitive sub-populations, such as children, (Jarosinska and Gee, 2007); sex, age, and immune conditions of the host; information physics; effects below the thresholds of "acute" impacts, such as tissue heating; non-linear dose/response relationships; "low dose" effects; and the effects arising from disturbing the balance between opposing elements in complex biological systems. The evidence on EMF needs to take full account of these realities, as well as of the methodological biases of Table 3.

1X. PUBLIC PARTICIPATION IN RISK ANALYSIS

Choosing an appropriate level of proof for a particular case is clearly based, *inter alia*, on value judgements about the acceptability of the costs, and of their distribution, of being wrong in both directions, i.e. of acting or not acting to reduce threatening exposures. This is why it is necessary to involve the public in decisions about serious hazards and their avoidance: and to do so for all stages of the risk analysis process.

Three of the "twelve late lessons" (number 5, number 9 and number 10) explicitly invite early involvement of the public and other stakeholders at all stages of risk analysis, a development which has been actively encouraged in many other influential reports during the last decade. (NRC 1994; US Presidential Commission on Risk Assessment and Risk Management 1997; Royal Commission on Environmental Pollution 1998; CEC Communication on the Precautionary Principle 2000; German Advisory Council on Global Change 2001).

The best available science is therefore only a necessary but not a sufficient condition for sound public policy making on potential threats to health and the environment. Where there is scientific uncertainty and ignorance "it is primarily the task of the risk managers to provide risk assessors with guidance on the science policy to apply in their risk assessments." (Christoforou, 2003). The content of this science policy advice, as well as the nature and scope of the questions to be addressed by the risk assessors, need to be formulated by the risk managers and relevant stakeholders at the initial stages of the risk analysis.

Involving the public in not only all stages of risk analysis, but also in helping to set research agendas and technological trajectories, (Wilsdon and Willis, 2004) is not easy. Many experiments, in both Europe and the USA, with focus groups, deliberative polling, citizens' juries, and extended peer review, (Funtovicz and Ravetz, 1990/92) are exploring appropriate ways forward.

The issue of time is also a critical issue for risk analysis and application of the precautionary principle. For example, the time from the first scientifically based early warnings (1896 for medical X rays, 1897 for benzene, 1898 for asbestos) to the time of policy action that effectively reduced damage was often 30-100 years. Some consequences of the failures to act in good time (e.g. on CFCs or asbestos) continue to cause damage over even longer time periods. For example, the ozone hole will cause many thousands of extra skin cancers in today's children but the cancers will only peak around the middle of this century because of the long latent period between exposure and effect. Such long-term but foreseeable impacts raise liability and compensation issues, including appropriate discount rates (if any) on future costs and benefits, which being value-laden choices. need also to be discussed by stakeholder groups. Again, experience in the climate change field with these long-term issues may be helpful in managing them with respect to electromagnetic fields (ELF and RF).

The wider involvement of stakeholders has also been recognised more recently by the International Risk Governance Council (IRGC, 2005) and the EU report on Science and Governance, (Wynne et al., 2007). Whether wider involvement of stakeholders results in better and more acceptable decisions needs to studied: early indications (Beierle, 2002), and lessons from history, suggests that is. In many cases several decades will be necessary to confidently judge outcomes, given latencies and complexities.

X. SOME EXAMPLES OF EARLY WARNINGS

The 14 case studies in the Late Lessons Report (EEA 2001) include examples some chemicals (tributylin or TBT, benzene, PCBs, CFCs, MTBE, SO_2 and Great Lakes pollution); two other pharmaceuticals (DES, and beef hormones); two physical agents (asbestos and medical x-rays); one pathogen (BSE); and Fisheries (overfishing).

The main issues discussed so far, such as the contingent nature of knowledge; ignorance and "surprises"; appropriate levels of evidence for policy actions; and public participation in risk analysis are critical to the successful application of both scientific knowledge and the precautionary principle to public policy-making. They are therefore relevant to discussions about the potentially new hazards that are now emerging e.g. from nanotechnology, (Royal Society 2003); from the non-ionising radiations arising from the use of mobile phones, (Stewart Reports 2000, 2004), and from endocrine disrupting substances or EDSs. (WHO, 2002).

With such newly emerging hazards it can be helpful to use historical examples to illustrate what a scientifically based early warning looks like as it is often difficult to properly recognise such warnings at the time they occur. A good example is that provided by the UK Medical Research Council's Swann Committee in 1969. They were asked to assess the evidence for risks of resistance to antibiotics in humans following the prolonged ingestion of trace amounts of antibiotics arising from their use as growth promoters in animal feed. (Edqvist and Pedersen 2001). They concluded that:

> *"Despite the gaps in our knowledge .. we believe … on the basis of evidence presented to us, that this assessment is a sufficiently sound basis for action .. The cry for more research should not be allowed to hold up our recommendations'….'sales/use of AFA should be strictly controlled via tight criteria, despite not knowing mechanisms of action, nor foreseeing all effect"*. (Swann 1969).

A. Antibiotics in Animal Feed

The Swann Committee also concluded that it would be more rewarding and innovative to improve animal husbandry as a means of encouraging disease free animal growth rather than to the cruder approach of diets containing antimicrobials. Despite the gaps in knowledge, the need for much more research, and considerable ignorance about the mechanisms of action, a sufficiency of evidence was identified and described by the Swann Report that justified the need for public authorities to restrict the possibility of exposures to antibiotics from animal growth promoters. This early warning was initially heeded, but was then progressively ignored by the pharmaceutical companies and regulatory authorities, who wanted more scientific justification for restricting anti-microbial growth promoters. However, in 1985 in Sweden, and then in the EU in 1999, the use of antibiotics as growth promoters was finally banned. Pfizer, the main supplier of such antibiotics in Europe, appealed against the European Commission banning decision, pleading, *inter alia*, an insufficiency of scientific evidence. They lost this case at the European Court of Justice (Case T-13/99-Pfizer 2002), a case which further clarified the proper use and application of the precautionary principle in circumstances of scientific uncertainty and of widespread, if low, public exposures to a potentially serious threat.

B. Lead in Gasoline

A US example of an early warning comes from the lead in gasoline story: a warning that was largely ignored for over 50 years, resulting in much damage to the intelligence and behaviour of children in America, Europe and the rest of the motorised world. Yandell Hendersson, Chair of the Medical Research Board, US Aviation Service, who had been asked to look at the scientific evidence on the possible hazards of tetraethyl lead during the temporary ban on lead in petrol, in 1925, concluded:

> *"It seems likely that the development of lead poisoning will come on so insidiously that leaded gasoline will be in nearly universal use … before the public and the government awakens to the situation"*. (Rosner and Markowitz, 2002).

Motorised societies would have gained much in dollars, brainpower and social cohesion had they heeded this foresight.

C. Tributylin (TBR) – A Marine Antifoulant for Ships

The case study on tributylin (TBT) and DES illustrate the surprises that arise from real life complexities and which may carry some lessons for the EMF debate. For example, the unfolding of the TBT story was accompanied by an increased appreciation of scientific complexity arising from the discoveries that adverse impacts were caused by very low doses (i.e. in parts/trillion); that high exposure concentrations were found in unexpected places e.g. in the marine micro-layer; and that bioaccumulation in higher marine animals, including sea-food for human consumption, was greater than expected. The early actions on exposure reduction in France and the UK in 1982-85 were based on a 'strength of evidence' for the 'association' only: knowledge about 'causality', **'**mechanisms of action' and other the complexities above came much later.

We were lucky in some ways with the TBT story: a highly specific, initially uncommon impact (imposex) was quickly linked to one chemical, TBT. This relatively easily identified linkage is not likely to be repeated for the more common and multi-causal impacts where, for example, neurodevelopmental diseases and dysfuntions, or common cancers, are the impacts under suspicion.

D. Diethylstilbestrol (DES)

Key lessons from the DES story are also instructive, as it provides the clearest example of endocrine disruption in humans. Diethylstilbestrol, commonly referred to as DES, is a synthetic estrogen . It was originally prescribed to prevent miscarriage, but did not. Later, sons and daughters of mothers given DES to prevent miscarriage developed cancers, reproductive tract anomalies, and had more pre-term babies themselves as a result. The effects of DES include the absence of visible and immediate teratogenic effects **not** being robust evidence for the absence of reproductive toxicity; and the **'**timing of the dose clearly determining the poison', in contrast to the 'dose determines the poison' dictum of Paracelsus. Timing is also relevant to other biological end points:

> *"the time of life when exposures take place may be critical in defining dose-response relationships of EDSs for breast cancer as well as for other health effects",* (WHO/IPCS, 2002).

Although the exposure levels were higher than the usual environmental levels of other EDSs, the DES story provides a clear warning about the potential dangers of perturbing the endocrine system with synthetic chemicals.

With over 20,000 publications, DES is now a well-studied compound, yet many doubts persist about its mechanisms of action. Since no dose-effect relationship has been found in humans, it cannot be excluded that DES could have been toxic at low doses, and that other less potent xenoestrogens could have similar effects.

If we still have few certainties about DES after so much time and research, what should our attitude be towards emerging hazards, such as other endocrine disrupting substances (EDSs) and EMF?

XI. CONCLUSION

The lessons of history from the EEA report, and subsequent debates and events, indicate that they have much relevance to the EMF issue, as well as to other emerging issues such as nanotechnology, (Royal Society, 2003) and endocrine disrupting substances or EDSs (WHO, 2002). The public health assessment of EMF could apply these lessons, approaches, terms of discussion and interpretations to the precautionary and preventative actions on the different parts of the EMF exposure problem.

There are of course large differences between smoking and EMF. The smoking hazard had at least 10 times the relative risk increase in the exposed population compared to the leukaemia risk from power line exposure; and the size of the smoking exposed population, and its exposure above that needed to generate a doubling of the risk, are both very much greater than with power lines. The larger relative risk for smoking and lung cancer seems to arise from comparing smokers with non, or never, smokers whilst the relative risk of 2 to 3 that arises between moderate and heavy smokers, or between second hand smokers and non smokers, is more relevant to the EMF issue, where there is an absence of unexposed controls. The lower relative risks of 2 or 3 for EMF are biased towards the null to unknown extent by the absence of such controls (Milham, 1998). However, the parallel between the slow recognition of the smoking hazard and power line EMF hazard is interesting.

The parallel with the history of X rays is also pertinent. The initial discovery, by Alice Stewart in the early 50s, that a few x rays of a pregnant woman in the sensitive period of her pregnancy gave a 2 fold excess of leukaemia, was greeted with much strident disbelief, particularly from the male doctors whose latest toy was under threat. It took another 20 years or so before her result became generally accepted, and only after several negative studies that were conducted in the early response to her study. Many studies of X rays in pregnant women now exist, and, as with the power line studies, the relative risk remains at about 2. (EEA, 2001) What will the history of EMF look like in 2020?

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SECTION 17

KEY SCIENTIFIC EVIDENCE AND PUBLIC HEALTH POLICY RECOMMENDATIONS

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July 2007

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I. KEY SCIENTIFIC EVIDENCE

Exposure to electromagnetic fields (EMF) has been linked to a variety of adverse health outcomes. The health endpoints that have been reported to be associated with ELF and/or RF include childhood leukemia, adult brain tumors, childhood brain tumors, genotoxic effects (DNA damage and micronucleation), neurological effects and neurodegenerative disease, immune system disregulation, allergic and inflammatory responses, breast cancer in men and women, miscarriage and some cardiovascular effects. Effects are not specifically segregated for ELF or RF, since many overlapping exposures occur in daily life; and because this is an artificial division based on frequencies as defined in physics that has little bearing on the biological effects. Both ELF and RF, for example have been shown to cause cells to generate stress proteins, a universal sign of distress in plant, animal and human cells.

The number of people exposed to elevated levels of EMF has been estimated in various studies, and there is general agreement among them. In the United States, few people have chronic or prolonged exposures over 4 mG (0.4 μT) (Kheifets et al, 2005b). Section 20 has information on average residential and occupational ELF levels. The highest exposure category in most all studies is $\geq$ 4 mG ($\geq$ 0.4 μT). Many people have daily exposures to ELF in various ways, some of them up to several hundred milligauss for short periods of time, but relatively few people with the exception of some occupational workers habitually experience ELF exposures greater than 1-2 mG (0.2 – 0.3 μT - App. 20-A).

The exposure of children to EMF has not been studied extensively; in fact, the FCC standards for exposure to radiofrequency radiation are based on the height, weight and stature of a 6-foot tall man, not scaled to children or adults of smaller stature. They do not take into account the unique susceptibility of growing children to exposures

(SCENIHR, 2007; Jarosinska and Gee, 2007), nor are there studies of particular relevance to children.

Differences in exposure patterns between infants, children and adults; 2) special susceptibilities of infants and children to the effects of EMF; and 3) interactions between chemical contaminants and EMF are lacking; as are studies on chronic exposure for both children and adults. There is reason to believe that children may be more susceptible to the effects of EMF exposure since they are growing, their rate of cellular activity and division is more rapid, and they may be more at risk for DNA damage and subsequent cancers. Growth and development of the central nervous system is still occurring well into the teenage years so that neurological changes may be of great importance to normal development, cognition, learning, and behavior. Prenatal exposure to EMF have been identified as possible risk factor for childhood leukemia. Children are largely unable to remove themselves from exposures to harmful substances in their environments. Their exposure is involuntary.

Like second-hand smoke, EMF is a complex mixture, where different frequencies, intensities, durations of exposure(s), modulation, waveform and other factors is known to produce variable effects. Many years of scientific study has produced substantial evidence that EMF may be considered to be both carcinogenic and neurotoxic. The weight of evidence is discussed in this report, including epidemiological evidence and studies on laboratory animals.

Relative risk estimates associated with some of these endpoints are small and the disease is fairly rare (for childhood leukemia, for example), For other diseases, the risk estimates are small but the diseases are common and EMF exposures at levels associated with increased risks are widespread and chronic so the overall public health impacts may be very large.

A. Weight of Evidence Assessment and Criteria for Causality

A weight-of-evidence approach has been used to describe the body of evidence between health endpoints and exposure to electromagnetic fields (ELF and RF).

The number and quality of epidemiological studies, as well as other sources of data on biological plausibility are considered in making scientific and public health policy judgments. Methodological issues that were considered in the review of the epidemiological literature include 1) quality of exposure assessment. 2) sample size of the study, which detects the power to detect an effect, 3) extent to which the analysis or design takes into account potential confounders or other risk factors, 4) selection bias, 5) the potential for bias in determining exposure. Assessment of the epidemiological literature is consistent with guidelines from Hill (1971), Rothman and Greenland (1998) and the Surgeon General's Reports on Smoking (US DHHS, 2004), and California Air Resources Board (2005). Factors that were considered in reaching conclusions about the weight of evidence overall included strength of the association, consistency of association, temporality, biological plausibility, dose-response and issues with non-linear dose-response, specificity and experimental evidence.

There is a relatively large amount of human epidemiological information with real world exposures, including data from occupational studies. There is less animal data in most cases, except for the genotoxicity studies. Human epidemiological evidence has be given the greatest weight in making judgments about weight-of-evidence, where the results across high quality studies give relatively consistent positive results. Meta-analyses of childhood leukemia, adult leukemia, adult brain tumors, childhood brain tumors, male and female breast cancer and Alzheimer's disease were relied upon in assessing the overall strength of epidemiological study results. Sections 5 – 15 provide analysis of the relevant scientific studies that are key evidence in making public health policy recommendations with respect to exposure to electromagnetic fields (both ELF and RF).

B. Summary of Evidence

1. Childhood Leukemia

Several meta-analyses have been conducted to assess risks of childhood leukemia from exposure to ELF. The results of these studies that combine or pool results of many individual studies (including studies that report both effects and no effects) consistently report increased risks.

Meta-Analysis: Studies of Childhood Leukemia and EMF

Greenland et al., (2000) reported a significantly elevated risk of 1.68 [95% CI 1.23-2.31] based on pooled results from 12 studies using a time-weighted average of exposure greater than 3 mG (0.3 µT). This is a 68% increased risk of childhood leukemia.

Ahlbom et al., (2000) reported a doubling of risk based on a meta-analysis of nine (9) studies. The results reported an elevated risk of 2.0 [95% CI 1.27-3.13] for EMF exposures equal to or greater than 4 mG (0.4 µT) as compared to less than 1 mG (0.1 µT)

Other Relevant Evidence

In 2002, the International Agency for Cancer Research (IARC) designated EMF as a "possible human carcinogen" or Group 2B Carcinogen based on consistent epidemiological evidence. The exposure levels at which increased risks of childhood leukemia are reported in individual studies range from above 1.4 mG or 0.14 µT (Green et al., 1999).
for younger children to age six (6) to 4 mG (0.4 µT). Many individual studies with cutpoints of 2 mG or 3 mG (0.2-0.3 µT)) report increased risks. Plausible biological mechanisms exist that may reasonably account for a causal relationship between EMF exposure and childhood leukemia.

Recurrence of Childhood Leukemia and Poorer Survival Rates with Continued EMF Exposure

Foliart reported more than a four-fold (450% increased risk) of adverse outcome (poorer survival rate) for children with acute lymphoblastic leukemia (ALL) who were recovering in EMF environments of 3 mG (0.3 µT) and above (OR 4.5, CI 1.5-13.8). Svendsen reported a poorer survival rate of children with acute lymphoblastic leukemia (ALL) in children exposed to 2 mG (0.2 µT) and above. These children were three times more likely (300% increased risk) to die than children recovering in fields of less than 1 mG (OR 3.0, CI 0.9.8). Children recovering in EMF environments between 1- 2 mG (0.1-0.2 µT) also had poorer survival rates, where the increased risk was 280% (OR 2.8, CI 1.2-6.2).

Higher Lifetime Cancer Risks with Childhood EMF Exposure

Lowenthal (2007) reported that children raised for the first five years in home environments exposed to EMF within 300 meters of a high voltage power line have a five-fold (a 500 percent increased risk of developing some kinds of cancers sometime in later life. For children from newborn to 15 years of age; it is a three-fold risk of developing cancer later in life (Lowenthal et al., 2007). There is suggestive evidence for a link between adult leukemia and EMF exposure.

Attributable Risk

Wartenberg estimates that 8% to 11% of childhood leukemia cases may be related to ELF exposure. This translates into an additional 175 to 240 cases of childhood leukemia based on 2200 US cases per year. The worldwide total of annual childhood leukemias is estimated to be 49,000, giving an estimate of nearly 4000 to 5400 cases per year. Other researchers have estimated higher numbers that could reach to 80% of all cases (Milham, 2001).

2. Childhood Brain Tumors

Childhood Brain Tumors

There is suggestive evidence that other childhood cancers may be related to EMF exposure. The meta-analysis by Wartenberg et al., (1998) reported increased risks for childhood brain tumors. Risks are quite similar whether based on calculated EMF fields (OR = 1.4, 95% CI = 0.8 – 2.3] or based on measured EMF fields (OR = 1.4, 95% CI = 0.8 – 2.4).

3. Adult Brain Tumors

Brain Tumors in Electrical Workers and in Electrical Occupations (Meta-analysis)

A significant excess risk for adult brain tumors in electrical workers and those adults with occupational EMF exposure was reported (Kheifets et al., 1995). This is about the same size risk for lung cancer and second hand smoke (US DHHS, 2006). A total of 29 studies with populations from 12 countries were included in this meta-analysis. The relative risk was reported as 1.16 (CI = 1.08 – 1.24) or a 16% increased risk for all brain tumors. For gliomas, the risk estimate was reported to be 1.39 (1.07 – 1.82) or a 39% increased risk for those in electrical occupations. A second meta-analysis published by Kheifets et al., ((2001) added results of 9 new studies published after 1995. It reported a new pooled estimate (OR = 1.16, 1.08 – 1.01) that showed little change in the risk estimate overall from 1995.

4. Brain Tumors and Acoustic Neuromas in Cell Phone and Cordless Phone Users (Meta-Analysis)

Glioma and Acoustic Neuroma

Hardell et al., (2007) reported in a meta-analysis statistically significant increased risk for glioma with exposure of 10 years or greater in persons using cell phones. Risks were estimated to be 1.2 (0.8 – 1.9) for all use; but when ipsilateral use was assessed (mainly on same side of head) it increased the risk of glioma to 2.0 (1.2 – 3.4) for 10 years and greater use.

For acoustic neuromas, Hardell et al., (2007) reported the increased risk with 10 years or more of exposure to a cell phone at 1.3 (0.6 – 2.8) but this risk increased to 2.4 (1.1 – 5.3) with ipsilateral use (mainly on the same side of the head). There is a consistent pattern of increased risk for brain tumors (glioma) and acoustic neuromas at 10 years and greater exposure to cell phones.

The meta-analysis by Lakhola et al., (2006) reported that brain tumor risk was 1.3 (0.99 – 1.9) for ipsilateral use of a cell phone, but no data was given for exposures at 10 years or greater (all exposures were of shorter duration).

The meta-analysis by Kan et al., (2007) reported "no overall risk" but found elevated risk of brain tumors (RR = 1.25, CI 1.01 – 1.54) $\geq$ 10 years, reinforcing the findings of other pooled estimates of risk. No estimates of increased risk with ipsilateral use were provided, which would have likely increased reported risks.

5. Neurodegenerative Diseases

Alzheimer's Disease and ALS

Evidence for a relationship between exposure and the neurodegenerative diseases, Alzheimer's and amyotrophic lateral sclerosis (ALS), is strong and relatively consistent. While not every publication shows a statistically significant relationship between exposure and disease, ORs of 2.3 (95% CI = 1.0-5.1 in Qio et al., 2004), of 2.3 (95% CI = 1.6-3.3 in Feychting et al., 2003) and of 4.0 (95% CI = 1.4-11.7 in Hakansson et al., 2003) for Alzheimer's Disease.

Hakansson et al., report more than a doubling of risk for ALS 2.2 (95% CI = 1.0-4.7).

Savitz et al., (1998) reports more than a tripling of risk for ALS (3.1, CI = 1.0 – 9.8).

6. Breast Cancer (Men and Women)

A meta-analysis by Erren (2001) on EMF and breast cancer reported pooled relative risks based on studies of both men and women. A total of 38 publications were reviewed; there were 23 studies on men; 25 studies on women; and 10 studies on both men and women. The pooled relative risk for women exposed to EMF was 1.12 (CI 1.09 – 1.15) or a 12% increased risk, Erren observed that variations between the contributing results are not easily attributable to chance (P = 0.0365). For men and breast cancer, he reported a fairly homogeneous increased risk (a pooled relative risk of 1.37 [CI 1.11 – 1.71]).

This analysis is well conducted. The results were stratified according to measured or assumed intensity of exposure to EMF; and the estimate of risk for the most heavily exposed group was extracted. Independent estimates of RRs were grouped according to gender, type of study (case-control and cohort), country where the study was conducted and method used to assess exposure. Pooled estimates of RRs and their 95% confidence intervals (CI) referring to various combinations of these factors were calculated according to appropriate statistical methods (Greenland, 1987). Misclassification possibilities were thoroughly assessed, and whether the results were sole endpoints or there were multiple endpoints in each study did not affect the RRs.

Erren qualifies his findings by discussing that latencies for cancers can be 20 to 30 years, Further, he notes that studies of total EMF exposures from both home, travel and workplace are rarely available, and these EMF sources are ubiquitous. Both could result in underestimation of risks. Another way in which risks might be masked is by variations in age of study participants. Forssen and colleagues (2000) reported no increased RRs for breast cancer in women of all ages when they combined residential and occupational EMF exposures (RR = 0.9, CI 0.3 – 2.7). However, when risks for the women younger than 50 years of age were separated out and calculated, the RR increased to 7.3 (CI 0.7 – 78.3) although with wide confidence intervals based on only four cases. Erren notes

"When possibly relevant exposures to EMF in the whole environment are assessed only partially, errors in the categorization of exposure status are likely to occur. If such misclassification is random and thus similar in subrgroups being compared (nondifferential), then the error will tend to introduce bias towards the null. Substantial random misclassification of exposures would then tend to generate spurious reports of 'little or no effect'. Note for example that estimates of smoking-associated lung cancer risks in the early 1950's could have been seriously distorted if exposure assessment had not considered smoking either at work or at home."

"Collectively, the data are consistent with the idea that exposures to EMF, as defined, are associated with some increase in breast cancer risks, albeit the excess risk is small."
Erren (2001)

7. Combined Effects of Toxic Agents and ELF

ELF and Toxic Chemical Exposures

There is also the issue of what weight to give the evidence for synergistic effects of toxic chemical exposure and EMF exposure. Juuilainen et al., (2006) reported that the combined effects of toxic agents and ELF magnetic fields together enhances damage as compared to the toxic exposure alone. In a meta-analysis of 65 studies; overall results showed 91% of the *in vivo* studies and 68% of the *in vitro* studies had worse outcomes (were positive for changes indicating synergistic damage) with ELF exposure in combination with toxic agents. The percentage of the 65 studies with positive effects was highest when the EMF exposure preceded the other exposure. The radical pair mechanism (oxidative damage due to free radicals) is cited as a good candidate to explain these results. Reconsideration of exposure limits for ELF is warranted based on this evidence.

II. FALLACIES AND ANSWERS IN THE DEBATE OVER EMF EVIDENCE

There are several arguments (false, in our view) that have been presented by those who minimize the strength of the relationship between exposure to both 50-60Hz ELF and RF EMFs. These are as follows:

A. "Only a small number of children are affected."

This argument is not correct because we do not know precisely how many children are affected. In 1988 Carpenter and Ahlbom attempted to answer this question based on the results of the New York State Powerlines Project and the results of the study of Savitz et al. (1988), and concluded that if the magnetic fields homes in the US were similar to those in Denver, Colorado fully 10 to 15% of US childhood leukemia (about 1,000 cases) could be associated with residential magnetic field exposure. They then concluded that exposure to magnetic fields from non-residential sources (particularly appliances) must be at least equal in magnitude, and that if so these two sources of exposure would account for 20-35% of childhood leukemia.

There have been several meta-analyses of the childhood leukemia data (Wartenberg, 1998; Greenland et al., 2000; Ahlbom et al., 2000). All have concluded that there is a significant association between residential exposure to magnetic fields and elevated risk of leukemia in children. Greenland et al. (2000)

performed a meta-analysis of 15 studies of magnetic field or wire code investigations of childhood leukemia, and calculated the attributable fraction of cases of childhood leukemia from residential magnetic field exposure in the US was 3%. Ahlbom et al. (2000) conducted a different meta-analysis that concluded there was a significant 2-fold elevation of risk at exposure levels of 4 mG (0.4 μT) or greater. Kheifets et al. (2006) attempted to calculate the attributable fraction of worldwide childhood leukemia due to EMFs, based on the meta-analyses of Ahlbom et al. (2000) and Greenland et al., (2000). They concluded that the attributable fraction of leukemia was between <1% to 4%. The recent WHO Environmental Health Criteria ELF Monograph #238 (2007) states "(A)ssuming that the association is causal, the number of cases of childhood leukaemia worldwide that might be attributable to exposure can be estimated to range from 100 to 2,400 cases per year. However this represents 0.2 to 4.9% of the total annual incidence of leukaemia cases, estimated to be 49,000 worldwide in 2000. Thus, in a global context, the impact on public health, if any, would be limited and uncertain."

These reports are important, in that they show consistency in there being a clearly elevated risk of leukemia in children with EMF exposure from power line fields in homes. These meta-analyses lead to the conclusion, reflected in the WHO report, that there is an association between childhood cancer and exposure to elevated magnetic fields in homes. We strongly disagree, however, with the overall conclusion that these calculations indicate that the fraction of childhood leukemia attributable to EMFs is so small as to not have serious public health implications.

There are several reasons why the WHO ELF Environmental Health Criteria Monograph conclusion is not justified. These studies all considered either only measured magnetic fields in homes or wire codes from power lines, ignoring exposure from appliances, wireless devices and all exposures outside of the home. Thus these metrics do not come close to accounting for any individual's cumulative exposure to EMFs. If residential magnetic fields cause cancer, then those from other sources will add to the risk. The failure to measure total EMF exposure would tend to obscure the relationship and lead to gross underestimation of the true relationship between exposure and disease. While the evidence for a relationship between exposure and childhood leukemia may be considered to be definitive at exposure levels of 3 or 4 mG (0.3 or 0.4 μT) or higher; there is evidence from some (but not all) of the other studies for an elevated risk at levels not greater than 2 mG (0.2 μT) (Savitz et al., 1988; Green, 1999). There is absolutely no evidence that exposures at lower levels are "safe", since persons with these exposures are usually the "control" group. Therefore this WHO statement fails to acknowledge the true magnitude of the problem, even when considering only childhood leukemia. The global attributable risk of childhood leukemia as a result of exposure to EMFs must be significantly greater than that calculated from consideration of only residential 50/60 Hz magnetic fields in studies where there is no unexposed control.

As detailed in other chapters in this report (Chapter 10), there is some evidence for a relationship between EMF exposure and brain cancers in children. We have almost no understanding of the mechanisms behind the development of brain cancers, and any cancer in a child is a tragedy. While evidence for a relationship between EMF exposure and childhood brain cancer is not as strong as for leukemia, it is of concern and deserves more study. Of even greater concern, given the clear evidence for elevated risk of childhood leukemia upon exposure to 50/60 Hz EMFs, is the relative lack of a comparable body of information on the effects of radiofrequency EMFs on the health of children. A recent study of South Korean children (1,928 with leukemia, 956 with brain cancer and 3,082 controls) living near to AM radio transmitters reports an OR of 2.15 (95% CI = 1.19-2.11) for risk of leukemia in children living within 2 km of the nearest AM transmitter as compared to those living more than 20 km from it (Ha et al., 2007). No relation was found for brain cancer. This study is consistent with the hypothesis that radiofrequency EMFs have similar effects to 50/60 Hz EMFs, but more study is needed. Since radiofrequency EMFs have higher energy than do power line frequencies, one might expect that they would be even more likely to cause disease. The enormous and very recent increase in use of cell phones by children is particularly worrisome. However there is little information at present on the long-term consequences of cell phone use, especially by children.

B. "There is insufficient evidence that adult diseases are secondary to EMF exposure."

It is correct that the level of evidence definitively proving an association between exposure to EMFs and various adult diseases is less strong that the relationship with childhood leukemia. However there are multiple studies which show statistically significant relationships between occupational exposure and leukemia in adults (see Chapter 11), in spite of major limitations in the exposure assessment. A very recent study by Lowenthal et al. (2007) investigated leukemia in adults in relation to residence near to high-voltage power lines. While they found elevated risk in all adults living near to the high voltage power lines, they found an OR of 3.23 (95% CI = 1.26-8.29) for individuals who spent the first 15 years of life within 300 m of the power line. This study provides support for two important conclusions: adult leukemia is also associated with EMF exposure, and exposure during childhood increases risk of adult disease. Thus protecting children from exposure should be a priority.

The evidence for a relationship between exposure and breast cancer is relatively strong in men (Erren, 2001), and some (by no means all) studies show female breast cancer also to be elevated with increased exposure (see Chapter 12). Brain tumors and acoustic neuromas are more common in exposed persons (see Chapter 10). There is less published evidence on other cancers, but Charles et al. (2003) report that workers in the highest 10% category for EMF exposure were twice as likely to die of prostate cancer as those exposed at lower levels (OR 2.02, 95% CI = 1.34-3.04). Villeneuve et al. (2000) report statistically significant elevations of non-Hodgkin's lymphoma in electric utility workers in relation to EMF exposure, while Tynes et al. (2003) report elevated rates of malignant melanoma in persons living near to high voltage power lines. While these observations need replication, they suggest a relationship between exposure and cancer in adults beyond leukemia.

Evidence for a relationship between exposure and the neurodegenerative diseases, Alzheimer's and amyotrophic lateral sclerosis (ALS), is strong and relatively consistent (see Chapter 12). While not every publication shows a statistically significant relationship between exposure and disease, ORs of 2.3 (95% CI = 1.0-5.1 in Qio et al., 2004), of 2.3 (95% CI = 1.6-3.3 in Feychting et al., 2003) and of 4.0 (95% CI = 1.4-11.7 in Hakansson et al., 2003) for Alzheimer's Disease, and of 3.1 (95% CI = 1.0-9.8 in Savitz et al., 1998) and 2.2 (95% CI = 1.0-4.7 in Hakansson et al., 2003) for ALS cannot be simply ignored.

In total the scientific evidence for adult disease associated with EMF exposure, given all of the difficulties in exposure assessment, is sufficiently strong that preventive steps are appropriate, even if not all reports have shown exactly the same positive relationship. While there are many possible sources of false positive results in epidemiological studies, there are even more possible reasons for false negative results, depending on sample size, exposure assessment and a variety of other confounders. It is inappropriate to discount the positive studies just because not every investigation shows a positive result. While further research is needed, with better exposure assessment and control of confounders; the evidence for a relationship between EMF exposure and adult cancers and neurodegenerative diseases is sufficiently strong at present to merit preventive actions to reduce EMF exposure.

C. "The risk is low."

This argument is incorrect because at present it is not possible to determine the magnitude of the risk. Clearly as far as EMFs are concerned there is no unexposed population. Therefore one can only compare groups with different levels of exposure. We can perhaps say with confidence that the elevated risk of leukemia from residential exposure of children to magnetic fields is "low" (meaning ORs in the range of 2-4), but this does not consider the child's exposure to appliances, exposure in automobiles and at daycare or school, exposures in playgrounds and at all of the other places that a child spends time. Even if the risk to one individual is low, the societal impact when everyone is exposed may be very significant.

In addition the exposure assessment is grossly inadequate, even in the best of studies. Most reports deal only with either characterization of the fields within residences or with job titles in occupational settings. Some studies attempt to quantitate other sources of exposure, such as frequency of cell phone usage or use of other appliances, but these studies almost always do not consider residential exposure from power lines. In no investigation has it been possible to follow the exposures of a large number of people over a number of years with accurate monitoring of total exposure to EMFs. This would of course be almost impossible to do for the very good reason that as a person moves through his or her environment the exposures vary from place to place and from moment to moment. However to truly and objectively determine the risk of exposure to EMFs it is essential to consider residential, occupational (or school) and recreational exposures to the full range of the electromagnetic spectrum, including appliances and wireless devices. This has not been accomplished in any study, and without such information it is not possible to determine the overall magnitude of the risk. It is possible, indeed likely, that upon consideration of both childhood and adult diseases that the risk is not low.

D. "There is no animal evidence".

It is correct that there is no adequate animal model system that reproducibly demonstrates the development of cancer in response to exposure to EMFs at the various frequencies of concern. McCann et al. (1997) reviewed the animal studies, and while they found most to be negative there were several that showed suggestive positive results. They also clearly identified issues that need to be improved in further animal carcinogenesis investigations. However Kheifets et al. (2005a) in a policy review noted that "even consistent negative toxicological data cannot completely overcome consistent epidemiological studies. First, a good animal model for childhood leukemia has been lacking. Second, particularly for ELF, the complex exposures that humans encounter on a daily basis and a lack of understanding of the biologically relevant exposure calls into question the relevance of exposures applied in toxicology. Another limitation of toxicologic studies is that animals cannot be exposed to fields that are orders of magnitude more powerful than those encountered by humans, decreasing their power to detect small risks." Further, they conclude that "(A)lthough the body of evidence is always considered as a whole, based on the weight of evidence approach and incorporating different lines of scientific enquiry, epidemiologic evidence, as most relevant, is given the greatest weight."

One positive animal study is that by Rapacholi et al. (1997), who demonstrated that lymphoma-prone transgenic mice developed significantly more lymphoma after exposure to 900 MHz fields (lymphoma being the animal equivalent of human leukemia) than did unexposed animals. More striking is the report from Denver, Colorado using the wire-code characterization originally developed by Wertheimer and Leeper (1979) showing that pet dogs living in homes characterized as having high or very high wire codes, as compared to those with low or very low wire codes or buried power lines, showed a OR of 1.8 (95% CI =

0.9-3.4) for development of lymphoma after adjustment for potential confounders, whereas dogs that lived in homes with very high wire codes had an OR of 6.8 (95% CI = 1.6-28.5) (Reif et al., 1995). This study is impressive because the exposure of the dogs reflects the environment in which exposure has been associated with elevated risk of human cancer in two independent investigations (Wertheimer and Leeper, 1979: Savitz et al., 1988).

It is curious that in many legal situations the courts are reluctant to accept only evidence that substance X causes cancer in animals without corresponding evidence in humans. In the case of EMFs we have strong evidence that EMFs cause cancer in human, but much less evidence from animal models. The US Supreme Court, in the case of Daubert vs. Merrell Dow Pharmaceuticals, effectively ruled that animal studies were not relevant to human health, and that the only admissible evidence must be from human epidemiological studies! While this is certainly not a justifiable conclusion, the situation with regards to EMF health effects is that we have strong evidence for human cancer from epidemiological studies, but do not have good evidence for cancer in experimental animals. But it is humans that we should be concerned about, not the laboratory rats.

E. “We do not know a mechanism.”

We do not know the mechanism of cancer in general, although we know a lot about cancer. It came as a major surprise to most scientists when Lichtenstein et al., (2000) reported that genetic factors play a minor role in causing most types of cancer, since it was commonly assumed that genetics was the major cause. However Lichtenstein et al. concluded from their study of identical twins that environmental factors were the initiating event in the great majority of cancers. This does not, of course, mean that genetic susceptibility to environmental contaminants is unimportant, but only that genetic factors alone do not result in cancer. We know mechanisms of action for some carcinogenic substances, but for most cancers we know neither the environmental trigger nor the mechanism of action. So there is no reason to negate the evidence that EMFs cause cancer just because we do not know a single mechanism to explain it’s mode of action.

We do not know the mechanism or cause for development of Alzheimer’s Disease or ALS. We do know that both are more common in individuals in certain occupations, and that exposure to certain metals appears to be associated with increased risk (Kamel et al., 2002; Shcherbatykh and Carpenter, 2007). In the case of Alzheimer’s Disease there are abnormalities of amyloid β and tau protein (Goedert and Spillantini, 2006), but very limited understanding of why or how they form. Neither the association with metals nor the presence of abnormal proteins constitutes a mechanism for cause of disease. So rather than discounting the relationship between EMF exposure and neurodegenerative diseases we should be using this information as a tool to better understand the etiology of these diseases.

There is clear evidence from animal and cell culture studies that ELF and RFR have biological effects. Furthermore, these effects occur at intensities commonly experienced by humans. We know a number of ways in which EMFs alter cell physiology and function, as detailed in various chapters in this report. EMFs affect gene transcription (Chapter 5 and 6), cause the synthesis of stress proteins (Chapter 7) and cause breakage of DNA, probably through generation of reactive oxygen species (Chapter 6 and 9 - Lai and Singh, 2004). Any one of these actions might be responsible for the carcinogenic and neurodegenerative actions of EMFs. However, as with many environmental agents, it would be a mistake to assume that there is only one target or mechanism of action. It is unlikely, for example, that the effects on the nervous system and behavior are secondary to exactly the same cellular targets and actions that lead to cancer. It is likely that there are multiple mechanisms of action leading to disease. But the lack of complete understanding of basic mechanisms does not alter the importance of the relationships.

F. Vested Interests: How They Shape the Public Health Debate

There is no question but that global implementation of the safety standards proposed in this report has the potential to not only be very expensive but also could be disruptive of life and economy as we know it if implemented abruptly and without careful planning. Action must be a balance of risk to cost to benefit. However, "deny and deploy" strategies by industry should not be rewarded in future risk assessment calculations. For example, if significant economic investments in the roll-out of risky technologies persist beyond the time that there is reasonable suspicion of risk available to all who look, then such costs should not be borne by ratepayers (in the case of new powerlines) or by compensating industry for bad corporate choices. Such investments in the deployment of new sources of exposure for ELF and RF should not count toward the balance sheet when regulatory agencies perform risk assessments. Mistakes may be made, but industry should make mid-course corrections to inform and protect the public, rather than deny effects pending "proof". Whether the costs of remedial action are worth the societal benefits is a formula that should reward precautionary behavior. Prudent corporate policies should be expected to address and avoid future risks and liabilities. Otherwise, there is no market incentive to produce safe (and safer) products.

The deployment of new technologies is running ahead of any reasonable estimation of possible health impacts and estimates of probabilities, let alone a solid assessment of risk. However what has been missing with regard to EMF has been an acknowledgement of the risk that is demonstrated by the scientific studies. As discussed in earlier sections, in this case there is clear evidence of risk, although the magnitude of the risk is uncertain, and the magnitude of doing nothing on the health effects cost to society is similarly uncertain. This situation is very similar to our history of dealing with the hazards of smoking decades ago, where the power of the industry to influence governments and even conflicts of interest within the public health community delayed action for more than a generation, with consequent loss of life and enormous extra health care costs to society.

Just because a problem is difficult to solve is not a reason to deny that a problem exists. In fact solutions to difficult issues usually can't be expected until the issues are known and creative thinking is brought to bear to find a solution.

The most contentious issue regarding public and occupational exposures to ELF and RF involves the resolute adherence to existing ICNIRP and IEEE standards by many countries, in the face of growing scientific evidence of health risks at far lower levels. Furthermore there is widespread belief that governments are ignoring this evidence. There are two obvious factors that work against governments taking action to set exposure guidelines based on current scientific evidence of risk. These are: 1) contemporary societies are very dependent upon electricity usage and RF communications, and anything that restricts current and future usage potentially has serious economic consequences and 2) the electric power and communications industries have enormous political clout and even provide support for a significant fraction of what research is done on EMF. This results in legislation that protects the status quo and scientific publications whose conclusions are not always based on only the observations of the research. It hinders wise public health policy actions and implementation of prevention strategies because of the huge financial investments already made in these technologies.

In 1989, in an editorial for Science Magazine, Philip H. Abelson called for more research into low-frequency electromagnetic fields. At that time, he confirmed that a US Office of Technology Assessment (OTA) study had determined that "*(o)verall, the evidence is too weak to allow firm conclusions either way*" but a policy of prudent avoidance strategy was suggested, Abelson defined this as "*to systematically look for strategies which can keep people out of 60 Hz fields*". Both policy actions were developed in the midst of scientific uncertainty, but rising concern for possible health impacts to the public. At that time, with high level of unknowns, the appropriate level of policy action was prudent avoidance or precautionary action. Nearly two decades later, the level of action warranted is higher – based on many new scientific publications confirming risks may exist – and justifying prevention or preventative action.

III. EMF EXPOSURE AND PRUDENT PUBLIC HEALTH PLANNING

• *The scientific evidence is sufficient to warrant regulatory action for ELF; and it is substantial enough to warrant preventative actions for RF.*

• *The standard of evidence for judging the emerging scientific evidence necessary to take action should be proportionate to the impacts on health and well-being*

• *The exposures are widespread.*

• *Widely accepted standards for judging the science are used in this assessment.*

Public exposure to electromagnetic radiation (power-line frequencies, radiofrequency and microwave) is growing exponentially worldwide. There is a rapid increase in electrification in developing countries, even in rural areas. Most members of society now have and use cordless phones, cellular phones, and pagers. In addition, most populations are also exposed to antennas in communities designed to transmit wireless RF signals. Some developing countries have even given up running land lines because of expense and the easy access to cell phones. Long-term and cumulative exposure to such massively increased RF has no precedent in human history. Furthermore, the most pronounced change is for children, who now routinely spend hours each day on the cell phone. Everyone is exposed to a greater or lesser extent. No one can avoid exposure, since even if they live on a mountain-top without electricity there will likely be exposure to communication-frequency RF exposure. Vulnerable populations (pregnant women, very young children, elderly persons, the poor) are exposed to the same degree as the general population. Therefore it is imperative to consider ways in which to evaluate risk and reduce exposure. Good public health policy requires preventative action proportionate to the potential risk of harm and the public health consequence of taking no action.

IV. RECOMMENDED ACTIONS

A. Defining new exposure standards for ELF

This chapter concludes that new ELF limits are warranted based on a public health analysis of the overall existing scientific evidence. The public health view is that new ELF limits are needed now. They should reflect environmental levels of ELF that have been demonstrated to increase risk for childhood leukemia, and possibly other cancers and neurological diseases. ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor. It is no longer acceptable to build new power lines and electrical facilities that place people in ELF environments that have been determined to be risky. These levels are in the 2 to 4 milligauss* (mG) range (0.2 – 0.4 μT), not in the 10s of mG or 100s of mG. The existing ICNIRP limit is 1000 mG (100 μT) and 904 mG (90.4 μT) in the US for ELF is outdated and based on faulty assumptions. These limits are can no longer be said to be protective of public health and they should be replaced. A safety buffer or safety factor should also be applied to a new, biologically-based ELF limit, and the conventional approach is to add a safety factor lower than the risk level.

While new ELF limits are being developed and implemented, a reasonable approach would be a 1 mG (0.1 μT) planning limit for habitable space adjacent to all new or upgraded power lines and a 2 mG (0.2 μT) limit for all other new construction. It is also recommended for that a 1 mG (0.1 μT) limit be established for existing habitable space for children and/or women who are pregnant (because of the possible link between childhood leukemia and *in utero* exposure to ELF). This recommendation is based on the assumption that a higher burden of protection is required for children who cannot protect themselves, and who are at risk for childhood leukemia at rates that are traditionally high enough to trigger regulatory action. This situation in particular warrants extending the 1 mG (0.1 μT) limit to existing occupied space. "Establish" in this case probably means formal public advisories from relevant health agencies. While it is not realistic to reconstruct all existing electrical distribution systems, in the short term; steps to reduce exposure from these existing systems need to be initiated, especially in places where children spend time, and should be encouraged. These limits should reflect the exposures that are commonly associated with increased risk of child hood leukemia (in the 2 to 5 mG (0.2 to 0.5 μT) range for all children, and over 1.4 mG (0.14 μT) for children age 6 and younger). Nearly all of the occupational studies for adult cancers and neurological diseases report their highest exposure category is 4 mG (0.4 μT) and above, so that new ELF limits should target the exposure ranges of interest, and not necessarily higher ranges.

Avoiding chronic ELF exposure in schools, homes and the workplace above levels associated with increased risk of disease will also avoid most of the possible bioactive parameters of ELF discussed in the relevant literature.

It is not prudent public health policy to wait any longer to adopt new public safety limits for ELF. These limits should reflect the exposures that are commonly associated with increased risk of childhood leukemia (in the 2 to 5 mG (0.2-0.5 μT) range for all children, and over 1.4 mG (0.14 μT) for children age 6 and younger). Avoiding chronic ELF exposure in schools, homes and the workplace above levels associated with increased risk of disease will also avoid most of the possible bioactive parameters of ELF discussed in the relevant literature.

B. Defining preventative actions for reduction in RF exposures

Given the scientific evidence at hand, the rapid deployment of new wireless technologies that chronically expose people to pulsed RF at levels reported to cause bioeffects, whicih in turn, could reasonably be presumed to lead to serious health impacts, is a public health concern. A public health action level that implements preventative action now is warranted, based on the collective evidence. There is suggestive to strongly suggestive evidence that RF exposures may cause changes in cell membrane function, cell communication, metabolism, activation of proto-oncogenes and can trigger the production of stress proteins at exposure levels below current regulatory limits. Resulting effects can include DNA breaks and chromosome aberrations, cell death including death of brain neurons, increased free radical production, activation of the endogenous opioid system, cell stress and premature aging, changes in brain function including memory loss, retarded learning, performance impairment in children, headaches and fatigue, sleep disorders, neurodegenerative conditions, reduction in melatonin secretion and cancers (Chapters 5, 6, 7, 8, 9, 10, and 12).

As early as 2000, some experts in bioelectromagnetics promoted a 0.1 μW/cm2 limit (which is 0.614 Volts per meter) for ambient outdoor exposure to pulsed RF, so generally in cities, the public would have adequate protection against involuntary exposure to pulsed radiofrequency (e.g., from cell towers, and other wireless technologies). The Salzburg Resolution of 2000 set a target of 0.1 μW/cm2 (or 0.614 V/m) for public exposure to pulsed radiofrequency. Since then, there are many credible anecdotal reports of unwellness and illness in the vicinity of wireless transmitters (wireless voice and data communication antennas) at lower levels. Effects include sleep disruption, impairment of memory and concentration, fatigue, headache, skin disorders, visual symptoms (floaters), nausea, loss of appetite, tinnitus, and cardiac problems (racing heartbeat), There are some credible articles from researchers reporting that cell tower -level RF exposures (estimated to be between 0.01 and 0.5 μW/cm2) produce ill-effects in populations living up to several hundred meters from wireless antenna sites,

This information now argues for thresholds or guidelines that are substantially below current FCC and ICNIPR standards for whole body exposure. Uncertainty about how low such standards might have to go to be prudent from a public health standpoint should not prevent reasonable efforts to respond to the information at hand. No lower limit for bioeffects and adverse health effects from RF has been established, so the possible health risks of wireless WLAN and WI-FI systems, for example, will require further research and no assertion of safety at any level of wireless exposure (chronic exposure) can be made at this time. The lower limit for reported human health effects has dropped 100-fold below the safety standard (for mobile phones and PDAs); 1000- to 10,000-fold for other wireless (cell towers at distance; WI-FI and WLAN devices). The entire basis for safety standards is called into question, and it is not unreasonable to question the safety of RF at any level.

A cautionary target level for pulsed RF exposures for ambient wireless that could be applied to RF sources from cell tower antennas, WI-FI, WI-MAX and other similar sources is proposed. The recommended cautionary target level is 0.1 microwatts per centimeter squared (μW/cm2)** (or 0.614 Volts per meter or V/m)** for pulsed RF where these exposures affect the general public; this advisory is proportionate to the evidence and in accord with prudent public health policy. A precautionary limit of 0.1 μW/cm2 should be adopted for outdoor, cumulative RF exposure. This reflects the current RF science and prudent public health response that would reasonably be set for pulsed RF (ambient) exposures where people live, work and go to school. This level of RF is experienced as whole-body exposure, and can be a chronic exposure where there is wireless coverage present for voice and data transmission for cell phones, pagers and PDAs and other sources of radiofrequency radiation. An outdoor precautionary limit of 0.1 μW/cm2 would mean an even lower exposure level inside buildings, perhaps as low as 0.01 μW/cm2. Some studies and many anecdotal reports on ill health have been reported at lower levels than this; however, for the present time, it could prevent some of the most disproportionate burdens placed on the public nearest to such installations. Although this RF target level does not preclude further rollout of WI-FI technologies, we also recommend that wired alternatives to WI-FI be implemented, particularly in schools and libraries so that children are not subjected to elevated RF levels until more is understood about possible health impacts. This recommendation should be seen as an interim precautionary limit that is intended to guide preventative actions; and more conservative limits may be needed in the future.

Broadcast facilities that chronically expose nearby residents to elevated RF levels from AM, FM and television antenna transmission are also of public health concern given the potential for very high RF exposures near these facilities (antenna farms). RF levels can be in the 10s to several 100's of μW/cm2 in residential areas within half a mile of some broadcast sites (for example, Lookout Mountain, Colorado and Awbrey Butte, Bend, Oregon). Like wireless communication facilities, RF emissions from broadcast facilities that are located in, or expose residential populations and schools to elevated levels of RF will very likely need to be re-evaluated for safety.

For emissions from wireless devices (cell phones, personal digital assistant or PDA devices, etc) there is enough evidence for increased risk of brain tumors and acoustic neuromas now to warrant intervention with respect to their use. Redesign of cell phones and PDAs could prevent direct head and eye exposure, for example, by designing new units so that they work only with a wired headset or on speakerphone mode.

These effects can reasonably be presumed to result in adverse health effects and disease with chronic and uncontrolled exposures, and children may be particularly vulnerable. The young are also largely unable to remove themselves from such environments. Second-hand radiation, like second-hand smoke is an issue of public health concern based on the evidence at hand.

V. CONCLUSIONS

• We cannot afford 'business as usual" any longer. It is time that planning for new power lines and for new homes, schools and other habitable spaces around them is done with routine provision for low-ELF environments . The business-as-usual deployment of new wireless technologies is likely to be risky and harder to change if society does not make some educated decisions about limits soon. Research must continue to define what levels of RF related to new wireless technologies are acceptable; but more research should not prevent or delay substantive changes today that might save money, lives and societal disruption tomorrow.

• New regulatory limits for ELF based on biologically relevant levels of ELF are warranted. ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor. It is no longer acceptable to build new power lines and electrical facilities that place people in ELF environments that have been determined to be risky (at levels generally at 2 mG (0.2 μT) and above).

• While new ELF limits are being developed and implemented, a reasonable approach would be a 1 mG (0.1 μT) planning limit for habitable space adjacent to all new or upgraded power lines and a 2 mG (0.2 μT) limit for all other new construction, It is also recommended for that a 1 mG (0.1 μT) limit be established for existing habitable space for children and/or women who are pregnant . This recommendation is based on the assumption that a higher burden of protection is required for children who cannot protect themselves, and who are at risk for childhood leukemia at rates that are traditionally high enough to trigger regulatory action. This situation in particular warrants extending the 1 mG (0.1 μT) limit to existing occupied space. "Establish" in this case probably means formal public advisories from relevant health agencies.

- While it is not realistic to reconstruct all existing electrical distributions systems, in the short term; steps to reduce exposure from these existing systems need to be initiated, especially in places where children spend time, and should be encouraged.

- A precautionary limit of 0.1 (μW/cm2 (which is also 0.614 Volts per meter) should be adopted for outdoor, cumulative RF exposure. This reflects the current RF science and prudent public health response that would reasonably be set for pulsed RF (ambient) exposures where people live, work and go to school. This level of RF is experienced as whole-body exposure, and can be a chronic exposure where there is wireless coverage present for voice and data transmission for cell phones, pagers and PDAs and other sources of radiofrequency radiation. Some studies and many anecdotal reports on ill health have been reported at lower levels than this; however, for the present time, it could prevent some of the most disproportionate burdens placed on the public nearest to such installations. Although this RF target level does not preclude further rollout of WI-FI technologies, we also recommend that wired alternatives to WI-FI be implemented, particularly in schools and libraries so that children are not subjected to elevated RF levels until more is understood about possible health impacts. This recommendation should be seen as an interim precautionary limit that is intended to guide preventative actions; and more conservative limits may be needed in the future.

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SECTION 19

GLOSSARY OF TERMS AND ABBREVIATIONS

Absorption. In radio wave propagation, attenuation of a radio wave due to dissipation of its energy, i.e., conversion of its energy into another form, such as heat.

Athermal effect. Any effect of electromagnetic energy on a body that is not a heat-related effect.

Blood–brain barrier. A functional concept developed to explain why many substances that are transported by blood readily enter other tissues but do not enter the brain; the "barrier" functions as if it were a continuous membrane lining the vasculature of the brain. These brain capillary endothelial cells form a nearly continuous barrier to entry of substances into the brain from the vasculature.

Conductance. The reciprocal of resistance. Expressed in siemens (S).

Conductivity: A property of materials that determines the magnitude of the electric current density when an electric field is impressed on the material.

Continuous wave. A wave whose successive oscillations are identical under steady-state conditions.

Current density. A vector of which the integral over a given surface is equal to the current flowing through the surface; the mean density in a linear conductor is equal to the current divided by the cross-sectional area of the conductor. Expressed in ampere per square metre ($A\ m^{-2}$).

Depth of penetration. For a plane wave electromagnetic field (EMF), incident on the boundary of a good conductor, depth of penetration of the wave is the depth at which the field strength of the wave has been reduced to 1/e, or to approximately 37% of its original value.

Dielectric properties: In the context of this document the properties of materials conductivity and permeability.

Dosimetry. Measurement, or determination by calculation, of internal electric field strength or induced current density, of the specific energy absorption, or specific energy absorption rate distribution, in humans or animals exposed to electromagnetic fields.

Electric field strength. The force (**E**) on a stationary unit positive charge at a point in an electric field; measured in volt per metre ($V\ m^{-1}$).

Electrosensitivity (Electrohypersensitivity): A working definition of EHS from Bergqvist et al. (1997) is “a phenomenon where individuals experience adverse health effects while using or being in the vicinity of devices emanating electric, magnetic or electromagnetic fields (EMFs)”.

Electromagnetic energy. The energy stored in an electromagnetic field. Expressed in joule (J).

Electric field strength (E): The magnitude of a field vector at a point that represents the force (F) on a charge (q). E is defined as E = F/q and is expressed in units of Volt per meter (V/m).

Electromagnetic field: Electromagnetic phenomena expressed in vector functions of space and time.

Electromagnetic radiation: The propagation of energy in the form of electromagnetic waves through space.

EMF. Electric, magnetic, and electromagnetic fields.

Exposure: Exposure occurs wherever a person is subjected to electric, magnetic or electromagnetic fields or contact currents other than those originating from physiological processes in the body.

Extra low frequency (ELF): Extra low frequency fields include, in this document, electromagnetic fields from 1 to 300 Hz. Alternately, **ELF-** Extremely low frequency where the European convention is extremely low frequncy, US is extra-low frequency.

Frequency modulation (FM): Frequency Modulation is a type of modulation representing information as variations in the frequency of a carrier wave. FM is often used at VHF frequencies (30 to 300 MHz) for broadcasting music and speech.

Far field. The region where the distance from a radiating antenna exceeds the wavelength of the radiated EMF; in the far-field, field components (**E** and **H**) and the direction of propagation are mutually perpendicular, and the shape of the field pattern is independent of the distance from the source at which it is taken.

Frequency. The number of sinusoidal cycles completed by electromagnetic waves in 1 second; usually expressed in hertz (Hz).

Impedance, wave. The ratio of the complex number (vector) representing the transverse electric field at a point to that representing the transverse magnetic field at that point. Expressed in ohm (S).

Magnetic flux density (B): The magnitude of a field vector at a point that results in a force (F) on a charge (q) moving with the velocity (v). The force F is defined by F = q*(v x B) and is expressed in units of Tesla (T).

Magnetic field strength (H): The magnitude of a field vector that is equal to the magnetic flux density (B) divided by the permeability (μ) of the medium. H is defined as H = B/μ and is expressed in units of Ampere per metre (A/m).

Magnetic permeability. The scalar or vector quantity which, when multiplied by the magnetic field strength, yields magnetic flux density; expressed in henry per metre (H $m^{!1}$). *Note:* For isotropic media, magnetic permeability is a scalar; for anisotropic media, it is a tensor quantity.

Microwaves: Microwaves are defined in the frame of this expertise as electromagnetic waves with wavelengths of approximately 30 cm (1 GHz) to 1 mm (300 GHz).

Milligauss (mG)

A milligauss is a measure of ELF intensity and is abbreviated mG. This is used to describe electromagnetic fields from appliances, power lines, interior electrical wiring.

Milliwatt (mW): A unit of power equal to 10^{-3}.

Microwatt (uW): A unit of power equal to 10^{-6}

Microwatts per centimeter squared (µW/cm2)

Radiofrequency radiation in terms of power density is measured in microwatts per centimeter squared and abbreviated (µW/cm2). It is used when talking about emissions from wireless facilities, and when describing ambient RF in the environment. The amount of allowable RF near a cell tower is 1000 µW/cm2 for some cell phone frequencies, for example.

Nanowatt (nW): A unit of power equal to 10^{-9} Watt.

Non – thermal effects (or athermal effects): An effect which can only be explained in terms of mechanisms other than increased molecular motion (i.e. heating), or occurs at absorbed power levels so low, that a thermal mechanism seems unlikely, or displays so unexpected a dependence upon some experimental variable that it is difficult to see how heating could be the cause.

Near field. The region where the distance from a radiating antenna is less than the wavelength of the radiated EMF. *Note:* The magnetic field strength (multiplied by the impedance of space) and the electric field strength are unequal and, at distances less than one-tenth of a wavelength from an antenna, vary inversely as the square or cube of the distance if the antenna is small compared with this distance. Near field exposures are unreliable for estimation of exposures by calculation. The can zero out or be additive and nearly infinite, thus creating problems for exposure assessment.

Non-ionizing electromagnetic radiation (NIER). Includes all radiations and fields of the electromagnetic spectrum that do not normally have sufficient energy to produce ionization in matter; characterized by energy per photon less than about 12 eV, wavelengths greater than 100 nm, and frequencies lower than 3×10^{15} Hz.

Occupational exposure. All exposure to EMF experienced by individuals in the course of performing their work. Safety limits are five times higher for allowable occupational exposures than for general public exposures in the US.

Permeability (μ): A property of materials that indicates how much polarisation occurs when an electric field is applied.

Permittivity. A constant defining the influence of an isotropic medium on the forces of attraction or repulsion between electrified bodies, and expressed in farad per metre (F $m^{!1}$); *relative permittivity* is the permittivity of a material or medium divided by the permittivity of vacuum.

Public Exposure. All exposure to EMF experienced by the general public excluding exposure during medical procedures and occupational work environments. Public exposure limits in the US are five times lower than for occupational exposures, where informed consent by employees is required.

Power Density. The power as measured in free space (ambient) as opposed to measured by SAR or specific absorption rate (within tissues or the body). The unit of measurement can be watts per square meter, milliwatts per square meter or microwatts per centimeter squared. Radiofrequency (RF). Any frequency at which electromagnetic radiation is useful for telecommunications, or broadcasting for radio and television. Frequency range is usually defined as 300 Hz (300 hertz) to 300 GHz (300 gigahertz).

Radiofrequency (RF): The frequencies between 100 kHz and 300 GHz of the electromagnetic spectrum.

Reasonance. The change in amplitude occurring as the frequency of the wave approaches or coincides with a natural frequency of the medium; whole body absorption of electromagnetic waves presents its highest value, i.e., the reasonance. for frequencies (in MHz or megahertz) corresponding to approximately 114/L where L is the height of the individual in meters. Reasonance can also be applicable to organs, tissues, or other body parts.

Specific Absorption Rate (SAR is measured in watts per kilogram or W/Kg)

SAR stands for specific absorption rate. It is a calculation of how much RF energy is absorbed into the body, for example when a cell phone or cordless phone is pressed to the head. SAR is expressed in watts per kilogram of tissue (W/Kg). The amount of allowable energy into 1 gram of brain tissue from a cell phone is 1.6 W/Kg in the US. For whole body exposure, the exposure is 0.8 W/Kg averaged over 30 minutes for the general public. International standards in most countries are similar, but not exactly the same.

Static electric field: Static fields produced by fixed potential differences.

Static magnetic fields: Static fields established by permanent magnets and by steady currents.

VDU: Video display units for computers, videos, TV and some measurement devices using cathode ray tubes

WI-FI: Stands for wireless fidelity. WI-FI systems create zones of wireless RF that allow access to wireless internet for computers, internet phone access and other wireless services. Access points that provide WI-FI to access Land Area Networks (LANs) can be installed on streets (for city-wide coverage) or indoors in buildings, Restaurants, hotels, coffee shops, airports, malls and other commercial enterprises are widely installing WI-FI. The range of typical WI-FI systems is about 300 feet.

WI-MAX: Stands for "Wireless interoperability for Microwave Access" and is a telecommunications technology aimed at providing wireless data over long distances. Like WI-FI, WI-MAX systems are designed to provide wireless access but over much broader geographic areas, with some systems transmitting signal up to 10 miles. Higher levels of RF are produced at the wireless transmission facilities than for WI-FI.s

Section 20 LIST OF ABBREVIATIONS

µT	microtesla
µW	microwatt
AC	Alternating current
ALS	Amyotrophic Lateral Sclerosis
AM	Amplitude modulation
B	Magnetic flux density
BBB	Blood-Brain-Barrier
CENELEC	European Committee for Electrotechnical Standardization
CI	Confidence Interval
CNS	Central Nervous System
CW	Continuous wave
DC	Direct current

DECT	Digital Enhanced Cordless Telephone
DMBA	7,12-dimethylbenz[a]anthracene
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
EHS	Electromagnetic hypersensitivity
ELF	Extra low frequency (also ELF-EMF)
EMF	Electromagnetic field
FM	Frequency Modulation
GSM	Global System for Mobile Communication
H	Magnetic field strength
HSP	Heat-shock proteins (stress proteins)
Hz	Frequency in Hertz
IARC	International Agency for Research on Cancer
IL	Interleukin
kg	Kilogram
kHz	Kilohertz
kV	Kilovolt
MF	Magnetic Field (sometimes MF-ELF)
MHz	Megahertz
ms	Milliseconds
mT	Millitesla
mG	Milligauss
mW	Milliwatt
nT	Nanotesla
nW	Nanowatt
NRPB	National Radiation Protection Board (HPA)
OR	Odds Ratio (measure of increased risk of disease)
REFLEX	European Research Program for Radiofrequency Hazards
RF	Radiofrequency Radiation (also written as RFR or RF-EMF)
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
TNO	Nederlandse Onderzoek (Netherlands Organisation Applied Scientific Research
UMTS	Universal Mobile Telephony System **UNEP** United Nations Environmental
VDT	Video display terminal (VDU – for computers, videos, TV, that use cathode ray tubes).
Wi-Fi	Short for wireless fidelity – wireless internet access - works for short-distances for cell phone and laptop computer access without wires.
WLAN	Wireless Local Area Network (wireless internet coverage usually up to 300’

provided by access points that create elevated radiofrequency radiation for that service zone.

WiMAX Worldwide Interoperability for Microwave Access (wireless service up to 10 miles in comparison to Wi-Fi that may serve 300' area)

WHO World Health Organisation

FCC The Federal Communications Commission (FCC) is an independent United States government agency, created, directed, and empowered by Congressional statute to oversee the regulation of radio and TV broadcasting and wireless technologies. It is not a health agency.

HPA Health Protection Agency (UK) that was formerly the National Radiation Protection Division Board). The Health Protection Agency (HPA) is an independent body that protects the health and well-being of the population. The Agency plays a critical role in protecting people from infectious diseases and in preventing harm when hazards involving chemicals, poisons or radiation occur.

DNA Deoxyribonucleic acid, or DNA is a nucleic acid molecule that contains the genetic instructions used in the development and functioning of all living things.

Melatonin Melatonin is a hormone produced in the brain by the pineal gland, It is a potent anti-oxidant that protects against oxidative damage from free radicals that can cause DNA damage.

Alzheimer's Alzheimer's disease is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities. As Alzheimer's progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations.

RFIAWG Radiofrequency Interagency Working Group (US) composed of members from federal agencies with some interest in radiofrequency radiation issues. This Working Group was made up of representatives from the US government's National Institute for Occupational Safety and Health (NIOSH), the Federal Communications Commission (FCC), Occupational Health and Safety Administration (OSHA), the Environmental Protection Agency (US EPA), the National Telecommunication and Information Administration, and the US Food and Drug Administration (FDA).

ICNIRP International Commission on Non-Ionizing Radiation. It is a body of independent scientific experts consisting of a main Commission of 14 members, 4 Scientific Standing Committees covering Epidemiology, Biology, Dosimetry and Optical Radiation and a number of consulting experts. This expertise is brought to bear on addressing the important issues of possible adverse effects on human health of exposure to non-ionising radiation.

SECTION 20 What are Ambient ELF and RF Levels?

Average Residential Exposures to ELF (Power Frequency Fields)

A nation-wide survey in the United States by Zaffanella et al (1993) collected engineering data on sources and levels of 60 Hz electric power magnetic fields that exist inside residences in the United States.

Approximately 1000 residences were randomly selected for the survey. The goals were to 1) identify all significant sources of magnetic field, 2) estimate for each source the percentage of residences where magnetic fields exceeded specified levels, 3) to determine the relation between magnetic field and sources and 4) to characterize the field varations in time.

The median field was identified as 0.5 mG and the average field was 0.9 mG. Thus, this confirms that average residential magnetic fields based on the 1000-home study is less than 1 mG.

Appliances produce magnetic fields but these diminish rapidly with distance (at $1/R^3$),

Power lines generally produce the largest average residential magnetic field when the entire living space of a residence and a 24-hour period are considered. Power line magnetic field exceeds 1 mG in 17%, exceed 2.5 mG in 9.5% and exceed 5 mG in 0.3% of all the residences surveyed.

Zaffanella (1998) conducted measurements to characterize typical EMF exposure levels in persons living in the United States - a study called the 1000-Person Study. Table A-S.2 shows that about half of all people in the US have EMF exposures at home under 0.75 mG; in bed are 0.48 mg; at school 0.60 mG; at work 0.99 mG; and 0.87 mG is the median EMF exposure for an average 24-hour day.

Table A-S.2

Table S.2 Descriptive Statistics for Different Activity Periods

Parameter	Home not in Bed	In Bed	Work	School	Travel	24-Hour
Number of Valid Data Sets	1011	996	525	139	765	1012
1st Percentile	0.10 mG	0.01 mG	0.14 mG	0.13 mG	0.13 mG	0.18 mG
5th Percentile	0.20 mG	0.08 mG	0.24 mG	0.18 mG	0.29 mG	0.27 mG
10th Percentile	0.27 mG	0.12 mG	0.30 mG	0.29 mG	0.41 mG	0.35 mG
25th Percentile	0.44 mG	0.24 mG	0.60 mG	0.35 mG	0.66 mG	0.51 mG
50th Percentile	0.75 mG	0.48 mG	0.99 mG	0.60 mG	0.98 mG	0.87 mG
75th Percentile	1.39 mG	1.24 mG	1.78 mG	1.01 mG	1.46 mG	1.41 mG
90th Percentile	2.49 mG	2.44 mG	3.32 mG	1.64 mG	2.18 mG	2.38 mG
95th Percentile	3.89 mG	3.63 mG	5.00 mG	1.77 mG	2.73 mG	3.38 mG
99th Percentile	9.50 mG	9.19 mG	13.5 mG	3.55 mG	5.43 mG	6.16 mG
Mean	1.29 mG	1.11 mG	1.73 mG	0.82 mG	1.22 mG	1.25 mG
Standard Deviation	2.54 mG	2.06 mG	3.09 mG	0.70 mG	0.99 mG	1.51 mG
Geometric Mean	0.80 mG	0.52 mG	1.03 mG	0.64 mG	0.96 mG	0.89 mG
Geometric Standard Deviation	2.50	3.52	2.57	2.06	2.03	2.18

In Sweden, Mild et al (1996) report that overall mean residential ELF exposures are 0.4 mG, and in Norway are 0.13 mG.

Average Occupational Exposures to ELF

Average occupational exposures in commercial office buildings are 1-2 mG or less and have been reported fairly consistently across numerous studies of exposure assessment (Table 1). Powerline and electrical workers have higher average occupational exposures from 10 mG to 16.6 mG.

Table A-2: Average Occupational Exposures to ELF

EMF RAPID Program – Questions and Answers, NIEHS, June 2002	
Office buildings (median)	0.6 mG
Support staff	0.5 mG
Professional staff	0.6 mG
Maintenance staff	0.6 mG
Visitors	0.6 mG
EMF RAPID Program Engineering Project #3 Executive Summary, May 1996	
Office building (average)	0.7 mG
Office building (median)	0.4 mG
Electric and Magnetic Field Fundamentals (EPRI Resource Paper, March 1994)	
Typical magnetic fields in offices	1 – 2 mG
Power line workers	10 mG
Occupational EMF Exposure Assessment (EPRI Resource Paper, February 1994)	
Office Worker Comparison Group	1.6 mG
All Occupationally Exposed Utility Workers	16.6 mG
Table 7 – Other Studies Cited	
Bracken Study (1990)	1.0 mG
Deadman Study (1988)	1.6 mG
Bowman Study (1992)	0.9 – 1.8 mG

Limits on Operation of Sensitive Electronic Equipment

Companies that manufacture or use equipment in nanotechnology and biotechnology and found 1.0 mG is generally the limit for proper operation of electron beam devices (mass spectrometers, scanning electron microscopes, lithography, etc) used in these technologies. Ten (10) milligauss (mG) is the EMF limit for normal computers – above 10 mG can introduce “computer jitter” and other problems.

What are Ambient Radiofrequency Radiation/Microwave Levels?

Prior to the rapid development of wireless communications for personal and business usage, RF power density levels were primarily related to AM, FM and television broadcasting signal in both urban and rural areas of the United States. Microwave frequencies used for wireless communications were negligible.

Original extra-planetary sources of microwave radiation were infinitesimally small, on the order of a billionth of a microwatt per centimeter squared (10^{-12} uW/cm^2). Human evolution took place without any appreciable exposure to microwave radiation from background sources. The human body has no evolutionary protection against microwave radiation, as it does for ultraviolet radiation from the sun (Johannson, 2000). Wireless voice and communications have introduced unprecedented levels of public exposure in the last decade.

Mantiply (1997) measured and reported common sources and levels of RF in the environment. He identified areas near cellular base stations on the ground near towers to be from 0.003 to 0.3 μW/cm2. Background level ambient RF exposures in cities and suburbs in the 1990's were generally reported to be below 0.003 μW/cm2.

Hamnerius (2000) reported that ambient RF power density measurements in twelve (12) large cities in Sweden were roughly ten times higher than in the United States for equivalent measurement locations by Mantiply in 1978 (when no cellular phone service existed in the US). He reported a total mean value of 26 measured sites in the study was 0.05 μW/cm2 and the median value was 40 μW/cm2. An office location with a base station nearby at about 300 feet distance tested 150 μW/cm2. A train station with antennas mounted indoors tested at about 3 μW/cm2. Both indoor and outdoor ambient RF power density measurements showed high variability depending on proximity to transmitting antennas.

Sage Associates reported on microwave frequency RF power density levels at outdoor locations both near and far from wireless antenna sites in the United States (Sage, 2000). Within the first 100-300 feet, power density levels have been measured at 0.01 to 3.0 μW/cm2. Elevated RF power density levels from a major wireless antenna site can often be detected at 1000 feet or more. Power density levels away from wireless antenna sites measure between 0.001 μW/cm2 to 0.000001 μW/cm2.

Vegetation often reduces signal (and therefore the reach of elevated RF exposures) but dry building materials used to visually screen wireless sites do not appreciably diminish signal transmission. Therefore, many sites that are “out-of-sight” because of stealth design can still produce elevated RF levels in nearby areas where people live, work and go to school. For purposes of this evaluation, a 10 dB attenuation has been incorporated to take building material shielding effects into account.

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SECTION 21: ACKNOWLEDGEMENTS

The BioInitiative Working Group gratefully acknowledges the assistance of Commonweal (Bolinas, California) who served as Fiscal Agent for financial support on this project; with special thanks to President Michael Lerner, Executive Director, Charlotte Brody, RN, Diane Blacker, Grants Manager for Commonweal, and to Eleni Sotos, Program Director for the Collaborative on Health and the Environment for her enthusiasm and guidance.

We thank Frieda Nixdorf, Administrative Specialist and Julia Varshavsky, Program Associate at the Collaborative for Health and the Environment for their administrative advice in setting up international conference calls for the BioInitiative Working Group.

We also wish to acknowledge and thank the Jenifer Altman Foundation and Ashley Iwanaga, Grants Administrator for support for media outreach and travel expenses; the EMR Policy Institute for serving as Fiscal Agent for our media outreach grant, and Dale Newton for his able work in setting up the BioInitiative website.

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Paula
Last Name: Cleveland
Mailing Address: 523 Huron Ave
City: Sheboygan
Country: United States
State or Province: WI
Postal Code: 53081
Organization Name: null

I was alarmed today by a letter to my local newspaper announcing your intention to drop maintenance funding for telephone land lines and switch all support to cell phone development. PLEASE DO NOT do this! I need my landline now and in the future. I CANNOT USE WIRELESS DEVICES or be around them because THEY MAKE ME SICK. I am sensitive to the frequencies employed by these devices, and I am finding it more and more difficult to isolate myself from them. I would never purchase a cell phone; I could not. Therefore, I am completely dependent on my telephone land line. Please do not make it less likely that this service may be discontinued. Do not change the distribution of maintenance funding.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Pamela
Last Name: Holbrook
Mailing Address: 218 NE 53rd St
City: Newport
Country: United States
State or Province: OR
Postal Code: 97365
Organization Name: null

Please, the switched telephone network must be maintained. The Architectural and Transportation Barriers Compliance Board (?the Access Board?), is the federal agency that administers the Americans with Disabilities Act. According to the Access Board, an estimated 3% of the population, or almost 10 million Americans, have electromagnetic sensitivities (access-board.gov/research/ieq/intro.cfm). They cannot use wireless technology and have difficulty using computers. They depend on the switched telephone network for voice communication. ?Universal Service? is not universal if it excludes 10 million people. Eliminating landlines will leave millions of Americans without even basic telephone service.
I do not tolerate this wireless technology either. We must ahvea choice.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Susan
Last Name: Molloy
Mailing Address: 8657 Hansa Trail
City: Snowflake
Country: United States
State or Province: AZ
Postal Code: 85937
Organization Name: null

See attached file(s)

RE: FCC proposal - Developing a Unified Intercarrier Compensation - FCC-2011-0078-0001

Please, do not replace existing landlines with wireless infrastructure.

Cell phones that are turned on around vulnerable individuals can be nerve-wracking and sickening. Also, cell phones can make people's wheelchairs and other assistive equipment malfunction.
Some crime victims, veterans, and children with PTSD, people with medical implants, and people who have certain neurological disabilities deserve to be able to use phones without getting sick.

Research on radiofrequency radiation exposure says it can alter blood glucose levels, weaken the blood-brain barrier, and evidently it can contribute to or even speed up cancer which already runs rampant in my family.

I cannot use any cordless or wireless phone for more than two minutes, every couple days maximum, or be near other people using theirs, without getting fierce migraines. This means nausea, can't eat, disorientation, exhaustion, increasing my anticonvulsant and painkillers, and likely a day or more isolated, probably lying on my bed.

I absolutely cannot carry a cell phone that is turned on to receive phone calls. A friend loaned me a cell phone for emergencies away from home so I can call out if there's no choice, like for when I get lost or real sick away from home, so somebody can come pick me up. But I do not, and expect to never, receive any calls on it because it hurts too much to have it turned on.

It is exhausting and frustrating to walk around trying to find a pay phone. It's especially hard when I have to locate a Circle K or 7-11 parking lot, practically the only places that still have pay phones, at night. If everybody is expected to use cell phones maybe even more pay phones will be phased out. I am elderly and disabled, and I need more, not fewer, public landline phones in secure, well-lit places for safety.

Please understand that making all phones be cell phones makes me more vulnerable, not less vulnerable.

Landlines are more private and using a mobile phone could make me vulnerable to criminals.

During power outages and natural disasters like snowstorms, which are common where I live, landlines are by far the most dependable even if they need repairs once in a while. We do not have cell coverage in many places I have to go because of the mountains, and for my purposes that is a good thing because more coverage would just hurt worse.

Teleconferencing
I rely on conference calling for medical appointments, worship, civic meetings, prayer meetings, and other things. Failure to get to have my conference calls would simply devastate me. What if the cell phone companies and the FCC leave me no choice but to hire help - to do probably untimely and possibly mixed up making and receiving of my calls?
I've read that VoIP costs more than $50 and I understand that it doesn't even adequately address the problems I have. It's way too expensive (money plus

getting sick) for me to experiment with equipment that is likely to not even help.

Wireless equipment can become overburdened during public emergencies, let alone that it can impose individual disasters for those of use who have no choice but to be out of the communications "mainstream."

Mobile phones fees keep going up.
Mobile phones and computers need constant repair, upgrades and replacement. For seniors and low-income citizens like me, living on approximately $700 in Social Security plus sometimes food stamps per month, cell phones and the modern skype computers are prohibitively costly even if they didn't hurt. What would you suggest I stop buying in order to afford such equipment, and tutoring, and the subscriptions for service, and house calls for repairs?

We grew up with landlines and know how to use them.
People with mental or other disabilities, dementia, or on certain medications and painkillers may not be able to learn how to use computer calls. I typically can turn on my battery operated computer for only one or two hours per day, and often maybe only for a couple days per week.

Cellphones require recharging. I had to recharge a cellphone in my house before and it was horribly painful (migraine, etc.) and disorienting. I have no option but to leave my house for at least two-three hours to recharge my toothbrush or computer battery. This is the only way I can operate such electronic equipment at all.

The FCC has the responsibility to facilitate accessible communications for all people.

Landline service is absolutely essential to many of us and must be preserved.

Removing landline service would deny us access to phone service, a fundamental and essential right and resource. This would also constitute a violation of the spirit and the language of the Americans with Disabilities Act and its recent amendments.

I want it to be against the law to eliminate landline service.

For a review of the information you need regarding access for those of us with disabling environmental sensitivities, see the website of the U.S. Architectural and Transportation Barriers Compliance Board (Access Board) at http://www.access-board.gov/research/ieq/intro.cfm

Thank you.
Susan R. Molloy, M.A.
8657 Hansa Trail
Snowflake, AZ, U.S.A. 85937

sm

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Robert
Last Name: Riedlinger
Mailing Address: RR2
City: Mission BC
Country: Canada
State or Province: B.C
Postal Code: V4S 1H9
Organization Name: null

I cannot use a wireless phone as I am hyper sensitive to EMF.We must preserve wired phones as many are like myself.

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Rosemary
Last Name: Jermann
Mailing Address: 3805 Lindell Blvd
City: St. Louis
Country: United States
State or Province: MO
Postal Code: 63108
Organization Name: N/A

For health reasons, some people must use landline telephones, not mobile phones. Therefore, please do not outlaw landline telephones.

Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Mara
Last Name: Bailey
Mailing Address: 275 Court Ave
City: Ventura
Country: United States
State or Province: CA
Postal Code: 93003
Organization Name: null

Please do not allow landlines to be discontinued. I, among many people are unable to use any form of wireless technology. I an extremely reactive to EFMs and even being around someone carrying a cell phone or being in an area that has wireless wifi gives me severe headaches and the longer I ma exposed the more intense the pain becomes and then more symptoms come up from my jaw aching to my rings ringing. I have to have an old fashioned phone with a cord, I had to give up my wireless dsl, wireless home phone and cell ph and can no longer use a wireless lap top all because my body has become so reactive to the EFMs. My grandmother,85, is hearing impaired and relies on her landlines for communications and community. My 75y yr old friend is visually impaired and can't use a cell ph. Were it were not for my rudimentary ability with a computer none of the 3 of us would be able to communicate our distress at learning losing our method of communication and connections to the out side world. there are many of us us are disabled and are unable to use and/ or too poor to afford a cell phone.
On behave of all of us who are unable to use or tolerate wirless PLEASE we BEG you not to discontinue our landlines, our safe means of connecting outside of our homes.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Liz
Last Name: Smentowski
Mailing Address: PO Box 356
City: Dolan Springs
Country: United States
State or Province: AZ
Postal Code: 86441
Organization Name: null

I am writing to express my strong feelings that the U.S. Government should NOT support or subsidize the dismantling of the existing switched telephone network. I suffer from disabling electromagnetic hypersensitivity (EHS), and I cannot use wireless phones or computers (my friend is typing this comment for me). Should the existing land-line telephone system go away, I would be left without the ability to communicate. In effect, I would lose my voice. Please don't do this to me or the millions of others who suffer from this very challenging medical condition.

Regards,
Liz Smentowski

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Margaret
Last Name: Patton
Mailing Address: 43 Plain Road
City: Wayland
Country: United States
State or Province: MA
Postal Code: 01778
Organization Name: none

Why eliminate landline phones when peer- reviewed scientific studies show biological effects of microwave radiation from various cellular devices at 0.01?W/cm2 while your FCC outdated standards are 1,000 ?W/cm2? How can you totally ignore the fact that you would be radiating children far above safe levels in their homes schools, everywhere. Do you have children or grandchildren? How could you only want cell phones when a 1998 study showed how people become addicted to cell phones? You need to upgrade the standards instead of eliminate landline phones. Our planet has too much microwave radiation now because of cell phones.

When we have winter storms in New England, the electricity goes out for days as falling trees and limbs hit electrical lines. My landline phones ALWAYS work when the electricity goes out. In a medical emergency, how does one use a dead cell phone?

Do you care that many young people only use cell phones, which is costly compared to a landline phone? The winners from the destruction of landlines phones are in the wireless industry and those who take industry contributions to help advance the industry?s plans. Some states are fighting to keep ?safe? utility meters out of homes. Here in Massachusetts, we are struggling to keep water meters from becoming wireless. Right now in my town, wired fire boxes that work perfectly well are being removed and not being replaced as the Fire Chief wants to use only wireless receivers at the Fire Station.

The issues in this proposal are complex and complicated. To deny people their landlines, you would endanger people?s health, take away their rights to use a public utility and allow a huge wireless industry to make vast sums of money by invading all American homes with this technology against people?s wills. This FCC action would be a government take-over of our democratic freedoms. Please protect our homes, children and lives by not eliminating landline phones.

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Title: Developing an Unified Intercarrier Compensation
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Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Scott
Last Name: Killingsworth
Mailing Address: PO Box 356
City: Dolan Springs
Country: United States
State or Province: AZ
Postal Code: 86441
Organization Name: null

Please do NOT dismantle the existing phone system! This would be catastrophic for those who suffer from Electromagnetic Sensitivity (EHS). These individuals--estimated at up to 10 million Americans--generally cannot use computers or cellsphones, and rely on land-line telephones for communications.

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Title: Developing an Unified Intercarrier Compensation
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Legacy Document ID:
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Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Sandra
Last Name: Kissam
Mailing Address: 1261 Union Avenue
City: Newburgh
Country: United States
State or Province: NY
Postal Code: 12550
Organization Name: null

I am writing to insist that ID FCC-2011-0078-0001 be totally scrapped.

Cell phones are a dangerous, expensive, and technically unsatisfactory means of communication. As a complement to land lines, they are bearable, but only as a supplemental means of communication.

The health impacts of the cell towers is an area of hot dispute and the facts indicate that they are dangerous to human health.

Creating the additional infrastructure to support exclusive cell phone use sounds like yet another gift to private corporate interests which, by the way, are very greedy with their customers, demanding contracts, fees for both incoming and outgoing calls, and other tricks that make it difficult for a consumer to have freedom of choice between available servers.

If you don't leave the current system alone and allow users the phone of their choice, including land line service, you are further degrading the environment, shaking individuals and businesses down for expensive fees, and inviting legal action against your proposals.

Sandra Kissam

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
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Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Linda
Last Name: Johnson
Mailing Address: 104 NW Parker
City: Grain Valley
Country: United States
State or Province: MO
Postal Code: 64029
Organization Name: null

The switched telephone network must be maintained.
There are many reasons, but here are several important ones: 1) According to the Access Board, almost 10 million Americans have electromagnetic sensitivities. They cannot use wireless technology and have difficulty using computers. They depend on the switched telephone network for voice communication. Eliminating landlines will leave millions of Americans without even basic telephone service. 2) Without the landlines, no communication will be available in the case of natural/cataclysmic disaster or terrorist activity that takes out wireless support systems such as satellites, towers, etc. 3) There are many poor people in rural areas and people in the mountains whose location make wireless technology useless.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: valentine
Last Name: Cotton
Mailing Address: 3 Headwater Lane
City: Newark
Country: United States
State or Province: DE
Postal Code: 19711
Organization Name: null

I am against eliminating landlines for phones. Cell phones are not always reliable and go down frequently. Also I am frightened of using cell phones too often as the "radiation" given off has been linked to brain tumors. I would NOT want to give up my landline.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Lynnell
Last Name: Rosser
Mailing Address: loni326@yahoo.com
City: Mesa
Country: United States
State or Province: AZ
Postal Code: 85207
Organization Name: null

Eliminating landline phones for people with Electrical Hypersensity is detrimental to their health. Many people with EHS cannot use a cell phone & a wired phone is the only means of communcation.

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Lisa
Last Name: Wertheim
Mailing Address: lisawertheim@yahoo.com
City: San Anselmo
Country: United States
State or Province: CA
Postal Code: 94960
Organization Name: Teens Turning Green

Do not replace existing landlines with wireless infrastructure until it is proven safe, secure, reliable and affordable!

Landlines are safe.
Children, people with medical implants, people with Radiofrequency Sickness, and people who don't want to increase their risk of cancer can use only landlines.

Research on radiofrequency radiation exposure indicates increased cancer incidence, altered blood glucose levels, weakened blood-brain barrier.

Many in the public cannot use any cordless or wireless phone without developing headaches that are often severe.

I urge you to keep Land Lines as the mode of communication!

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Sharon
Last Name: Wirtz
Mailing Address: 161-D Calle Ojo Feliz
City: Santa Fe
Country: United States
State or Province: NM
Postal Code: 87505
Organization Name: null

I strongly object to the proposed elimination of land line phones. They are safe, secure, reliable, and affordable. They are more appropriate to seniors.

I am concerned about possible health effects of using wireless phones especially for children. A friend, a young relater, was always glued to his cell phone. He now had been fighting debilitating brain and neck cancers in the area just behind where his cell phone was. I have read literature to support this probable cause. I have another friend who gets a spell of shaking and dizziness whenever a cell phone goes off or is turned on near her. I have seen this happen to her when she has no idea a cell phone is in the vicinity until she begins to shake. Several doctors she has consulted confirm the cause. If her land line phone was eliminated, she would have no phone service.

Because we can't prove the safety of cell phones, I have chosen to go without one, and I am able to conduct my life and go about my business just fine without it. I want the choice to continue to use my land line phone. I do not want the expense of multiple cell phones. I resent that the government thinks they know which type of phone I should use.

Land line phones are more reliable, especially in an emergency.

Land line phones are more environmentally responsible. It seems that people are always replacing their cell phones because they quit working or get lost. The old phones go in the land fill. My very old land line phone has worked well for years and years.

I know many people who keep misplacing their cell phones, especially seniors. A land line phone stays put. Knowing where the phone is located is important to everyone, especially seniors, especially in an emergency.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Matthew
Last Name: Tessmann
Mailing Address: 1632 Saamis Dr N.W. #318
City: Medicine Hat
Country: Canada
State or Province: Alberta
Postal Code: t1c2b3
Organization Name: null

Radiation alone is reason enough to oppose this bill - it seems cellular phone radiation is rampantly ubiquitous and virtually impossible to avoid as it is - you are literally taking what refuge sensitive and health conscious people have and effectively dissolving it. Please do not consider this bill and keep an open and safe landline system.

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Katie
Last Name: Alvord
Mailing Address: PO Box 516
City: Houghton
Country: United States
State or Province: MI
Postal Code: 49931
Organization Name: null

See attached file - in brief, I have two main comments re this proposal:

1.The analog circuit-switched telephone network must be maintained to provide universal phone service, especially because many electrically sensitive people are unable to use anything else.

Our household is one of many that continues to rely on an analog landline. We CANNOT use cell phones, digitized phones, or wireless technologies because my husband has multiple chemical sensitivities as well as electrical sensitivities. He is unable to stand even within a few feet of a cell phone without experiencing symptoms, and is also limited as to how much he can use a computer. He relies heavily on an analog landline, and we know others like him.

Figures from the ADA Access Board suggest that 10 million Americans might be similarly electrically sensitive. Phasing out analog landlines would thus create a large new class of telecomm-unserved Americans. To prevent this from happening, and to continue universal phone service, you must continue to maintain the analog circuit-switched telephone network.

2.Any public funds directed to broadband should go only to fixed fiber-optic installations and not to wireless networks, for reasons of economy, national security, and public health.

I support using fiber optics instead of wireless for at least the following reasons:

-Fiber-optic cable is more cost-effective.
-Fiber-optic cable is less subject to security disruptions than wireless networks.
-Fiber-optic cable is superior for public health reasons. A growing body of evidence suggests that wireless technologies affect physiology and health. Continuing to expand wireless despite such findings risks public health.

Again, I urge you:
1.	To maintain universal phone service, you must maintain the analog circuit-switched telephone system.
2.	For better economy, national security, and public health, direct any public funds for broadband to fiber-optics, NOT to wireless.

Thank you.

To the FCC:

I write regarding your proposed changes to the Universal Service Fund, to express my support for use of fiber-optics as opposed to wireless broadband, and especially to urge you to continue maintaining the analog circuit-switched telephone network. I have two main comments in response to this proposed rulemaking:

1.The analog circuit-switched telephone network must be maintained as part of providing universal phone service, for several reasons but especially because many electrically sensitive individuals are physically unable to use anything else.

Our household is one of many that continues to rely on an analog landline. We CANNOT use cell phones, digitized phones, or wireless technologies in our home because my husband has been diagnosed with multiple chemical sensitivities as well as electrical sensitivities. He is unable to stand even within a few feet of a cell phone without experiencing symptoms, and is also limited as to how much he can use a computer. For his own independence, he relies heavily on an analog landline, and we know many others like him.

The ADA Access Board cites figures suggesting that 10 million Americans might be similarly electrically sensitive. Many if not all of these people are, like my spouse, unable to use wireless or digital phone service or computers. Like us, they rely on the analog circuit-switched phone network of traditional landlines for most if not all of their telecommunications needs. In addition, I understand that some people with medical implants use traditional landlines because cell phones sometimes interfere with the operation of their implants.

Phasing out the switched phone network would thus create a large new class of telecomm-unserved Americans. To prevent this from happening, and to continue the standard of universal telephone service, you must continue to maintain the analog circuit-switched telephone network – for our household and for others like us.

Our analog network of traditional landlines also continues to play an important communications role for the general public. These landlines continue to be important in emergencies; when the power grid goes down, cellphone service can be disrupted while traditional circuit-switched landlines continue to operate. Weakening or eliminating the traditional landline system could thus create communication gaps that could risk public safety; maintaining the landline network gives us a better overall public safety communications system.

2.Any public funds directed to broadband as part of this rulemaking should go only to fixed fiber-optic installations and not to wireless networks, for reasons of economy, national security, and public health.

In general, the wireless industry is booming and does not need additional money from the government. In cases such as underserved rural areas where the government determines that some sort of public funding is necessary, I support using fiber optics instead of wireless for at least the following reasons:

1-Fiber-optic cable is more cost-effective especially in the long run because its greater capacity means it does not become obsolete as quickly as wireless, and it does not need frequent replacement. I also understand that it needs less maintenance.
2-Fiber-optic cable is better for national security as it is less subject to disruption than wireless networks. As noted by the Coalition for Local Oversight of Utility Technologies (CLOUT), wireless networks are vulnerable to hacking wherever a potential cyber-terrorist can pick up a signal. Fiber-optics do not have this same level of vulnerability.
3-Fiber-optic cable is superior for public health reasons. Not only does it have less effect on the electrically sensitive, but there is a growing body of evidence suggesting that wireless technologies affect the physiology of all living cells, including those in the human nervous system. For instance, earlier this year a highly-respected study appearing in the Journal of the American Medical Association found that cell phones accelerate glucose metabolism in brain cells. Previous studies have found that wireless frequencies can increase permeability of the blood-brain barrier, allowing potentially damaging large proteins into the brain; break DNA strands; alter white blood cell activity in schoolchildren; reduce sperm quality; increase the risk of acoustic neuromas; increase the risk of salivary gland tumors; and have other effects too numerous to list here. Continuing to expand the wireless network in the face of such scientific findings risks a potentially significant deterioration of public health.

Again, I urge you:

1. To maintain universal phone service, you must maintain the analog circuit-switched telephone system.
2. For better economy, national security, and public health, direct any public funds for broadband to fiber-optic installations, and not to wireless.

Thank you for your consideration. I would appreciate being added to your notification list. I can be reached at ktalvord@gmail.com via my dial-up service accessed over an analog phone line, as well as via postal mail.

Sincerely,

Katie Alvord

Please Do Not Reply To This Email.

Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Julie
Last Name: Laffin
Mailing Address: 200 church
City: Harvard, IL
Country: United States
State or Province: IL
Postal Code: 60033
Organization Name: re|shelter

There are many people in our country for whom cell phone use is not an option because of severe health consequences when exposed to a variety of electronic frequencies. For these individuals and their families, land lines are the only option they have. Many of these people are disabled from electrical sensitivities and are already living in rural areas because of they need to avoid electrosmog as much as possible. Taking away their use of the telephone would not only be an enormous disservice to them because of their forced isolation away from mainstream society but could also be considered an endangerment to them as they would become cut off from all forms of contact with the outside world including emergency medical services. WE MUST KEEP WIRED LAND LINES AVAILABLE to those who currently need them because of health reasons and for all individuals who wish to limit their exposure to cell phone use.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Vivian
Last Name: Koroghlian
Mailing Address: 1404 Santa Rosa Drive
City: Santa Fe
Country: United States
State or Province: NM
Postal Code: 87505
Organization Name: null

I am objecting to the proposed elimination of landline telephones, which I think are absolutely necessary for reliable emergency service, for seniors who cannot learn new technology, for EMF-sensitive individuals, for people who do not want to expose themselves to the cancer risk posed by cellphones (which has been documented in research studies) and simply to preserve freedom of choice. I also think it is very wasteful to eliminate existing infrastructure which works well for wired phone service and to flood our environment with more wireless antennas, the hazards of which we have not studied enough. The FCC must resist pressure from telecommunication corporations whose only interest is profits. Your mandate is to serve the needs of people, not corporations.

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Kiki
Last Name: Panos-Sperazza
Mailing Address: 21-34 37th street
City: astoria
Country: United States
State or Province: NY
Postal Code: 11105
Organization Name: null

Eliminating landline telephones is absurd! As a resident of Astoria, New York, several years ago my neighborhood experienced a severe black-out that lasted for a week. The only way we were able to communicate with others was through our landline telephones. And what about the risks associated with cell phones/cell towers? Research is still being conducted as to the effects of cell phone use and cell towers upon our health and our environment. Furthermore, you have many elderly that do not like to use cell phones so their only means of communication is via their land lines.
DO NOT ELIMINATE LANDLINES!

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Dana
Last Name: Davis
Mailing Address: 210 Vallejo Street, Suite C
City: Petaluma
Country: United States
State or Province: CA
Postal Code: 94952
Organization Name: null

I am completely opposed to eliminating land lines! My land line works when the power is out. My mom has a cell phone and Vonage service, but I helped her get a basic land line in case of emergencies. When power is out, you can't' charge your cell phones, so it's dangerous in emergency situations to not have access to land lines.

I also am seriously concerned about health risks of wireless technology. I use my cell phone rarely. We need to have land lines to protect people's health. Read the research that is NOT funded by industry groups. That tells the truth.

Please ensure that all Americans have access to land lines without adding ANY additional costs to them.

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: bob
Last Name: coleman
Mailing Address: namelocrp1@frontier.com
City: durham
Country: United States
State or Province: NC
Postal Code: 27707
Organization Name: null

i haveheard that there is a proposal to eliminate land lins in this country.
i am strongly against this because of a number of reasons; 1- There is mounting scientfiic proof that cell phones are the cause of cancer in the brain... near the ear (see www.mercola.com) and 2- there are many people in this country who DON"T own cell phones!
The telephone is a PUBLIC SERVICE and should be protected.

respectfully,
Bob Coleman
namelocrp1@frontier.com
www.bobcolemanlmbt.com

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Martha
Last Name: Roberts
Mailing Address: 1740 Madera St.
City: Berkelery
Country: United States
State or Province: CA
Postal Code: 94707
Organization Name: null

I am deeply concerned that the FCC is considering the "Unified Intercarrier Compensation" rule.

This proposal would cause many cellular transmission towers to be built in rural areas, effectively end landline service in those areas and, eventually, end landlines all over America. Given that the health effects of microwave radiation are, at the very least, unknown (as admitted by a representative of the cell phone industry during recent Congressional hearings), this is a dangerous direction for the FCC to go. The telecommunications industry insists there are no adverse health effects, but, hidden in the small print of their consumer information packets are warnings not to put the phone against the ear or to wear it next to the body --clearly they know otherwise. A recent review of published research indicates that independently funded studies found serious health effects, while studies that were funded by the industry found none.

I am one of the 10 million Americans, as estimated by the Americans with Disabilities Access Board, who have electromagnetic sensitivities. Since early 2008, I have experienced frequent headaches, digestive disturbances, and insomnia. I have measured ambient radiation levels in my area and have found they are well above levels that research shows can cause these symptoms (Altpeter, 1995, 1997) When I am in an environment where EMF radiation is low for at least 24 hours, my headaches go away but I still have insomnia and digestive problems. I personally know how debilitating EMF can be.

Like other Americans with electrical sensitivities, I depend on landline service. Eliminating landlines will leave millions of EMF sensitive Americans in rural areas without even basic telephone service. This will be a violation of the Americans with Disabilities Act. And there will be "no place to hide" for sufferers like me.

I implore the FCC to consider the health of this nation, and not enact this rule.

Sincerely,
Martha Robe

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Ariel
Last Name: Barfield
Mailing Address: PO Box 36688
City: Tucson
Country: United States
State or Province: AZ
Postal Code: 85740
Organization Name: null

Many people, including myself, are hypersensitive to to the electromagnetic radiation emitted by cell phones. We react in a variety of different ways, including jitteryness, nausea, fatigue, and heart beat irregularities.

Please Do Not take away our land lines.

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: K.
Last Name: Farewell
Mailing Address: 1613 S. Escondido
City: Escondido
Country: United States
State or Province: CA
Postal Code: 92025
Organization Name: null

Do not dismantal the land lines in the U.S. It is a violation of personal choice, health concerns about cell phones and wireless technology which I do not chose to be around.

As to National Security, I also believe this is a VERY bad choice. In recent years, with black-outs of satelites, cellular and internet shutdowns, that in some cases have taken whole sections of the country down, NO ONE WITH INTERNET OR CELL phones had any access to the outside world and were completely cut off. This is a terrible idea where cyberspace terrorism is concerned.

We NEED land lines to ALWAYS have a solid back up in emergencies. Also, millions of people with disabilities can not use cellular technology or be exposed to it. (My wife is one of these people and has severe disabilities to cellular signals and all digital technology.) Poverty also plays a role in keeping land lines.

Anyway you cut it, this is a bad, bad plan and I am voicing my objections to it immediately.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Brian
Last Name: Wahlig
Mailing Address: 911 W.Theresa LN.
City: Glendale
Country: United States
State or Province: WI
Postal Code: 53209
Organization Name: null

Do not eliminate landline telephones. I do not use or wish to use cell phones. It's very difficult to use the small controls for many people including the elderly and disabled. I also do not want to be forced to use something that can emit possible harmful radiation. Not all new technology is good technology and I(and many) believe that the harmful effects(cancer) of using this technology will keep appearing in the coming decades.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Leslie
Last Name: Sheridan
Mailing Address: P.O. Box 726
City: Clearlake
Country: United States
State or Province: CA
Postal Code: 95422-0726
Organization Name: null

DO NOT ELIMINATE LANDLINES AND TAKE AWAY OUR CHOICE! CELL PHONES ARE DANGEROUS AND I WILL NOT EXPOSE MYSELF TO THEIR RADIATION!

THE FACT THAT YOU ARE SO IN BED WITH INDUSTRY AS TO SUGGEST THIS, AFTER AIDING THE REMOVAL OF SO MANY PAY PHONES ALREADY IS DISGUSTING, AND MORE EVIDENCE THAT CORPORATIONS ARE RUNNING WHAT USED TO BE THE PEOPLE'S DEMOCRACY!

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Steve and Juleen
Last Name: Ross
Mailing Address: HC3 Box 1039
City: Tucson
Country: United States
State or Province: AZ
Postal Code: 85739
Organization Name: null

Some members of our family are part of a growing population in this country who experience pain or other physical problems in close proximity to certain electronic devices. This includes computers, large screen TVs, and wireless communication devices. For example, after watching a movie on TV, Juleen has numbness in her legs and feet. This discomfort is relieved by turning off the TV. When Juleen sits for an extended period at the computer -- she feels cognitively impaired and exhausted.

For this reason we do not use any wireless phones or other devices in our house and only have a cell phone for emergency use.

We wonder if these kinds of health concerns are on the radar of officials who are considering the replacement of all corded phones with broadband services. IT WOULD BE PATENTLY UNFAIR AND CONTRADICTORY TO THE PHILOSOPHY OF INCLUSIVENESS BEHIND THIS BROADBAND PROPOSAL, TO EXCLUDE THOSE WHOSE MEDICAL NECESSITY REQUIRES THE USE OF CORDED PHONES. This would create an unbearable burden for people like us who are already severly limited in social interaction by our illnesses.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Lisa
Last Name: Maiocco
Mailing Address: 109 Lowell RD #312
City: North Reading
Country: United States
State or Province: MA
Postal Code: 01864
Organization Name: null

I am strongly opposed to the elimination of land lines.

My first concern : cell network reliability & reception is not good enough in large regions of the USA. I live in Mass. now, but in 4 of the 5 Maine towns I lived in, the cell service was not reliable. We needed a landline for international calls, conference calls, job phone interviews, or calls where a misunderstanding due to bad reception would be serious (negotiating a house repair, call with your lawyer, confidential business calls, etc).

I also lived in Pennsylvania from 2005 to Jan 2011, and had similarly poor cell phone reception in Pike Township, Boyertown PA 19512. We only had service from one particular tower due to the hilly terrain. If that tower was on the fritz, our house cell service would be unreliable for a few days.

My 2nd concern is aging relatives. . My elderly mother in law has a cell phone but she often can?t find it or has forgotten to charge it.

My 3rd concern is cellular network performance during emergency situations. I personally experienced 3 ice storms. In each of these 3 storms, my house lost electricity for more than 3 days: these were 1998 (Maine) and 2006 / 2011 (Pennsylvania). Thankfully, our land lines continued to work and were *invaluable* during these times of freezing temperatures with no heat and no electricity.

Also, in times of an earthquake or nuclear event or 9/11, land lines are invaluable way to find elderly relatives that need to be rescued

My 4th concern is that for private calls (like a medical consultation or a psychotherapist?s call to a client) cell phones do not have adequate privacy.

My 5th concern is health ? the electric fields from cell phones are measurable / concerns of long term cell usage. (Note: I am an engineer)

Internet phone services do not solve these problems- they won?t work without electricity. Jamming the internet could be done by terrorist groups in conjunction with another attack event
Thanks L Maiocco

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Janet
Last Name: Palmer
Mailing Address: PO Box 1318
City: Patagonia
Country: United States
State or Province: AZ
Postal Code: 85624
Organization Name: null

I am one of 10 million disabled Americans who have electromagnetic sensitivities so sever that I must communicate via a land line telephone. I cannot use wireless phones.

My business (and thus self support) depends on my being on the telephone for hours a day.

PLease continue to subsidize rural telephone line service to the full extent so that we who are disabled can continue to have access as the disability laws mandate.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Carol
Last Name: McEwan
Mailing Address: 11665 NW 800 Road
City: Appleton City
Country: United States
State or Province: MO
Postal Code: 64724
Organization Name: null

Please maintian the switched telephone network. Nearly 10 million Americans, my son included, have electromagnetic sensitivities and depend upon the switched telephone network for voice communication. There are also many other reasons landline telelphones need to be continued!

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Andrea
Last Name: Pinnow
Mailing Address: 8333 Rockin Ranch Trail #4
City: Snowflake
Country: United States
State or Province: AZ
Postal Code: 85937
Organization Name: null

I would like to express my concern for the FC's plan to eliminate landlines. I developed electromagnetic hypersensitivity in November 2007, after living in highrise apartment building that had multiple cell towers on it. I have been unable to use a cell phone since November 2007. I lost by ability to be on a computer in August 2009, as my condition worsened with exposure to Wifi. Seven months ago, I moved across the country to escape the eletropollution of the Washington D.C. area and to try to regain my health. If land lines are eliminated, I would be unable to use a phone and thus work.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: SUSAN
Last Name: FOSTER, MSW
Mailing Address: 15957 AVENIDA CALMA
City: Rancho Santa Fe
Country: United States
State or Province: CA
Postal Code: 92091
Organization Name: medical writer & author

As someone who is electro-hypersensitive and also a consumer with a cardiac abnormality that puts me at risk when I am around cell phones and other RF (microwave) radiation emitting devices, I am strongly opposed to the US making landlines obsolete.

With a population that is approximately 10% electro-hyper-sensitive, I find it incredibly dangerous and in direct opposition to the goals of the Americans with Disabilities Act to do away with landlines which are the only form of communication individuals with EHS should use.

I cannot use a cell phone safely and therefore you7 would be cutting off my only form of SAFE communication.

I see doing away with landlines as serving the telecom industry only. Private citizens with EHS and cardiac abnormalities requiring pacemakers would be at a great disadvantage.

Thank you,
Susan Foster, MSW

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Sandra
Last Name: Mesa
Mailing Address: PO Box 2024
City: Snowflake
Country: United States
State or Province: AZ
Postal Code: 85937
Organization Name: null

I Sandra Mes request of you not to remove land line phone service, it will affect my health to use cellular phone or digital service.

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FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: K.
Last Name: Racki
Mailing Address: Rt. 2
City: Whitehall
Country: United States
State or Province: WI
Postal Code: 54773
Organization Name: Rural US Citizen

It has come to my attention that the FCC is beginning to consider phasing out land-line telephone service. PLEASE KEEP LAND LINES!!! We live in a rural area and have spotty cell service at best, and cannot depend on cell phones even in town half the time. While cell phones may be the "in" thing these days, many of us can only really depend on our land-line phone service. Please keep the Universal Service Fund focused on making sure all Americans have dependable access to real phones. IN AN EMERGENCY IT'S OUR LAND LINE WE CAN DEPEND ON.
Another issue is the fact that a growing number of people - around 10 million - are having adverse reactions to cell phones - ie ...ELECTROMAGNETIC SENSITIVITIES. A friend of mine has become quite INCAPACITATED due to exposure to wireless emissions and cell phones. If she didn't have a land-line phone, she'd be cut off totally from any sort of distance communication other than the postal service or similar services.
It's also been interesting trying to find someone's cell phone number if you don't carry it with you all the time. With land-lines, you can look it up in the book!! I have found that to be a real draw-back re: cell phones.
While it may be helpful at times to use a cell phone - yes I do have one - I never ever count on having it work where we are, and many places I go in our area.
So, I urge your agency to KEEP LAND LINES and do NOT eliminate wired, land-line phone service.
Thank you for your attention.
kr

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: nancy
Last Name: friedman
Mailing Address: po box 7
City: Bronx
Country: United States
State or Province: NY
Postal Code: 10464-0007
Organization Name: null

FCC,
Landlines SHOULD NOT be tampered with for a number of reasons.
1-In emergencies cellular telephones are inadequate and fail. I know first-hand because I was at The World Trade Center on the morning of 9-11. Not only was the cellular phone failure my experience but Mayor Rudy Giulliani went searching for a land line for the very same reason. The cellular service is unreliable, especially in an emergency situation as is stated in the movie "The Day After Tomorrow" and can be confirmed by
any cell phone user.
2- Not everyone can use cell phones and not everyone can afford cell phones and not everyone wants to carry cell phones for a myriad of reasons including the fact that RF radiation is generated from them and has ill-effects on the human body.
3- Many public places have already removed their land lines and not only is it inconvenient but it is inadvisable. Cell phones have batteries that run down and the service is compromised as a result.
4- Telephone service needs to be close to 100% reliable and cell phones fall far short of this, particularly because they are battery operated.
5- Cellular phone usage by the general population is a new use of this technology and the impact on the public is untested at this point. It would be extremely careless and cavalier for FCC to make a decision to dispense with the land lines at this point in time.
All of these points must certainly be understood by the FCC and I am very surprised that the possibility of doing away with the switched telephone network is even a consideration.

Nancy Friedman

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: John
Last Name: Schwindt
Mailing Address: PO Box 841
City: Meadview
Country: United States
State or Province: AZ
Postal Code: 86444
Organization Name: null

I request that the FCC does not dismantle telephone land lines. I am entirely dependent on the land lines because of my disability - i.e., sensitivity to digital electronics such as cell phones and computers. Eliminating land lines would leave me helpless in a remote rural area.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Joni
Last Name: Aarden
Mailing Address: 340 Farragut Ave
City: Kensington
Country: United States
State or Province: MD
Postal Code: 20895
Organization Name: null

Please keep our landlines working! There is not enough long-term evidence to support the full safety of cell phones. According to The Architectural and Transportation Barriers Compliance Board ("the Access Board"), an estimated 3% of the population, or almost 10 million Americans, have electromagnetic sensitivities (http://www.access-board.gov/research/ieq/intro.cfm). They cannot use wireless technology and have difficulty using computers. They depend on the switched telephone network for voice communication. "Universal Service" is not universal if it excludes 10 million people. Eliminating landlines will leave millions of Americans without even basic telephone service.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Elysia
Last Name: Drew
Mailing Address: 12
City: North Yarmouth
Country: United States
State or Province: ME
Postal Code: 04097
Organization Name: null

The switched telephone network must be maintained. I am one of at least 10 million Americans who are electro-hypersensitive and get incredibly sick from using cordless phones, WiFi, cellphones etc. When I'm near Smart Meters or cellphones, I get migraines, insomnia, intense full-body pain, nausea, chest pain, and since Smart Meters were installed in my town, I've had 8x more seizures than usual, and a stroke-like episode. Electrosensitivity is recognized under the Americans with Disabilities Act. Smart Meters have made me so sick that I can no longer tolerate my cellphone and recently had to move to an off-grid cabin, where my ONLY means of communication is a landline. To reduce electrosensitivity symptoms, I deliberately have NO electricity in my home, and heat it only with a woodstove. I do not have electricity to power a computer, even if I did have broadband access, nor can I tolerate using a computer for long enough to make the calls I need to make. I am disabled and don't have the income to pay for Internet, nor do I want it in my home. I depend on the switched telephone network for communication, and should I have an emergency, my landline is the only way I can make a phone call. "Universal service" is NOT universal if it excludes 10 million people. Eliminating landlines will leave millions of Americans without even basic telephone service. Please maintain the switched telephone network. My health and basic rights, as well as the health and basic rights of millions of others, are at stake.

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Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Ruth
Last Name: Hartman
Mailing Address: 1075 Poplar
City: Boulder
Country: United States
State or Province: CO
Postal Code: 80304
Organization Name: null

There are many people who don't want to use cell phones and I am among them. I don't have one and never want to. A land line is perfect for my home and business. PLEASE do not eliminate this choice for me and many others.
The last thing we need are more cell phone towers and more microwave radiation harming the population.
We must have a choice!

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Public Comments on Developing an Unified Intercarrier Compensation:========

Title: Developing an Unified Intercarrier Compensation
FR Document Number: 2011-04399
Legacy Document ID:
RIN:
Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Deborah
Last Name: Boye
Mailing Address: PO Box 1238
City: Dolan Springs
Country: United States
State or Province: AZ
Postal Code: 86441
Organization Name: null

I am writing to tell you that using my telephone land line is by far my preferred method of communication. My jawbone aches within a minute of using a cell phone, I get a slight headache, and feel tired. I also do not like sitting in front of my computer to talk to someone. I spend enough hours in front of this electronic field and need a break from it. The telephone connected to the land line does not give me any of these adverse feelings.

Please consider the impact of EMF's on the body and don't dismantle the land line system!

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Publish Date: 3/2/2011 12:00:00 AM

Submitter Info:
First Name: Willa
Last Name: Bower
Mailing Address: 555 Ocean Ave.
City: Monterey
Country: United States
State or Province: CA
Postal Code: 93940
Organization Name: null

Addendum to previous comment.

Beyond the 10 million Americans who are unable to use cell phones or VOiP, there are further compelling reasons that landlines are necessary to our communications network. Cell phone and VOiP DO NOT WORK all the time in all circumstances. For the many millions of people who live in mountainous areas, cell phone DO NOT WORK. Millions of others DO NOT UNDERSTAND how to use cell phones or computers (and therefore VOiP). As a computer teacher, I know this for a fact. Some people just don't learn computers, let alone software. That leaves them without a phone and phones are absolutely necessary to survival as well as normal functioning.

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Submitter Info:
First Name: Ernest
Last Name: Stiltner
Mailing Address: 181 Sawmill Road
City: Jamestown
Country: United States
State or Province: CO
Postal Code: 80455-9721
Organization Name: Rocky Mountain Environmental Health

Completely kill proposal FCC-2011-0078-0001 to phase out landlines. This would be a long-term public disaseter for our entire society. This proposal would remove any communication ability for the some one percent of the population that has electrical hypersensivity (EHS).
This proposal flouts both the wording and the spirit of the Americans with Disabilities Act (ADA) and its recent extensions.
There is extensive independent reseacch that long-term exposure cause a wide vqariety of serious health problems.
A r4ecent study in Sweden before and aftercell service showed serious declines in overall health throughout the population.
People with MCS who cannot tolerate any electromagnetic radiation exposrure would be completely unable to communcate - a more and more vital need in our society.

And fix this sloppy web site. It is inexcusable to disable the back arrow key for only one example. And enable people to email a copy of their comments to themselves for their recor4ds. And on.\

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Submitter Info:
First Name: Mona
Last Name: Linstromberg
Mailing Address: 831 E. Buck Creek Rd
City: Tidewater
Country: United States
State or Province: OR
Postal Code: 97390
Organization Name: null

For over a decade I have been assisting communities in fighting the inappropriate siting of cell phone towers near homes and schools. I am well versed in the FCA of 1996, and its total disregard of environmental impact of radio frequency radiation emitted by this technology, especially harmful to the still developing bodies (brains) of children.

Using cell phones is an individual's choice. Having a cell tower next to one's home or school is not,as it affects entire communities. Just remember cigarettes when contemplating the larger (negative) impact on the health of our nation. During the landuse process in approving the siting of towers, those on the ground representing the providers have commented (not on the record). that,if I was worried about the towers emitting radio frequency radiation, I should really be worried about cell phones.

Those of us who have landline phones need to be able to make a choice as well. Do not impinge on our rights to put ourselves out of harms way as much as possible. As it is, public payphones are a dying breed. Private landlines are an essential way to communicate. Also, I do not want to support the development of broadband systems with the fees I pay on my landline.

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Submitter Info:
First Name: Lynn
Last Name: Gores
Mailing Address: 3283 Crosswind Ct.
City: Colgate
Country: United States
State or Province: WI
Postal Code: 53017
Organization Name: None

Re: The FCC proposal to expand cell phone coverage areas and to allow the reduction or elimination of land lines: I do not believe that this proposal is based on any hard research that cell phones are safe over the long term, especially for children. I myself can seldom use one as it gives me headaches and other symptoms. My land line has proven safe and reliable over many decades. It has not given me problems. I feel my communications are secure with a land line and it is reasonably priced for the service given. Please allow more time for comments on this issue and for any existing research to be more carefully considered. Thank you.

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Submitter Info:
First Name: Irene
Last Name: McKay
Mailing Address: 250 Ridge Ave.
City: Evanston
Country: United States
State or Province: IL
Postal Code: 60202
Organization Name: null

From what I've read there is a real danger in the use of cell phones and brain damage/cancer, and I believe that the use of home phones with land lines are needed. Therefore, to do away with the land line would create additional health problem now and in the future, especially for the younger generation.

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Submitter Info:
First Name: Willa
Last Name: Bower
Mailing Address: 555 Ocean Avenue
City: Monterey
Country: United States
State or Province: CA
Postal Code: 93940
Organization Name: null

The switched telephone network must be maintained. The Architectural and Transportation Barriers Compliance Board (?the Access Board?), is the federal agency that administers the Americans with Disabilities Act. According to the Access Board, an estimated 3% of the population, or almost 10 million Americans, have electromagnetic sensitivities (access-board.gov/research/ieq/intro.cfm). They cannot use wireless technology and have difficulty using computers. They depend on the switched telephone network for voice communication. ?Universal Service? is not universal if it excludes 10 million people. Eliminating landlines will leave millions of Americans without even basic telephone service. These 10 million people will be put at continuing risk of harm and death in case of all emergencies including: war, crime, health crises, accidents, natural disasters, etc. This choice is absolutely unacceptable, unethical, and immoral. It will feed the insatiable greed of the few at great cost to 10 million Americans who pay their taxes and uphold the laws of this country. You can and must do better for all Americans than this.

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Submitter Info:
First Name: m
Last Name: campbell
Mailing Address: edward st
City: charlottetown
Country: Canada
State or Province: Prince Edward Island
Postal Code: c1a5e4
Organization Name: null

do not abandon the regular system of phone lines
- many still need and need to use these important 'landlines'
- and would be cutof
- and furthur disabled from/by communications

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Submitter Info:
First Name: Terry
Last Name: Siemens
Mailing Address: P.O. Box 1318
City: Sacramento
Country: United States
State or Province: CA
Postal Code: 95812
Organization Name: null

To: FCC (Document ID FCC-2011-0078-0001)
Re: Elimination of Land Lines Proposed by AT&T
Date: April 18, 2011
Dear Sirs:
I am concerned about AT&T's proposal to eliminate land lines. This proposal, if enacted, would adversely effect my health, my safety and my ability to professionally and personally communicate with others.

I have a severe medical case of vasovagal episodes resulting from exposure to radio frequency microwave fields. I cannot use digital land lines, nor can I use the 4G Fios offered to ratepayers in my neighborhood.

I have asked Verizon for a medical exception to use the existing copper lines in my home. Verizon has refused. Yet others in my neighborhood who continue to use their copper landlines are able to do so, because they initiated their service before I did.

Therefore, at this time, I have no phone service in my home, which will continue for the foreseeable future. Unless some outside government agency recognizes this injustice and demands that Verizon respond to the needs of those of us with ongoing health impairments, I will continue to remain disinfranchised from my community and my profession. Furthermore, these circumstances require that I drive over twenty miles to use a landline.

Again, this situation is detrimental to my heath, my safety and my professional productivity. Please do not eliminate the use of landlines. In addition, please ask Verizon to reinstate the use of the existing copper land lines in my home.

Sincerely,
Terry Siemens

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Submitter Info:
First Name: Deborah
Last Name: Kopald
Mailing Address: PO Box 998
City: Fort Montgomery
Country: United States
State or Province: NY
Postal Code: 10922
Organization Name: null

See attached file(s)

The FCC should abandon latest proposal which encompasses promoting wireless last-mile coverage of broadband infrastructure: FCC 11-13. I have appended notes from the 289 page report http://www.fcc.gov/Daily_Releases/Daily_Business/2011/db0209/FCC-11-13A1.pdf at the end of this note that explain how the FCC plan amounts to the first steps in the abolition of land-line service.

Meanwhile, the science on cell phones is clear that there is a problem. Here are the cliffnotes:

* Congressional hearings held in '08+'09 enumerated dangers of using a cell phone
* last month's NIH report explained that brain scans showed that 50 minutes on a cell phone drastically changed brain metabolism in the area of the brain linked with judgment and repression of rage
* the $25 million CTIA study in the mid-nineties found double strand DNA breaks, acoustic neuroma increases and cell micronucleation
* the European REFLEX studies in 2000 found deleterious biological effects from cell phone radiation
* the German company T-Mobil did a survey of existing literature finding negative consequences to cell phone use
* the Austrian reinsurance industry refused to reinsure wireless companies after finding decreased test performance by adults who used a cell phone for a couple of hours and irregularities in test tube samples of blood exposed to cell phone radiation
* Appendix 2 of the WHO INTERPHONE Report released in April, 2010 links 10 years of cell phone to a doubling of gliomas
* The U.S. Presidential Cancer Panel Report called wireless technologies likely carcinogens
* the UK and Israeli governments have informed the public **not** to abandon their landlines; Israel recommends corded landlines and not portable phones (which emit microwave radiation).
* major scientists including David Carpenter of the Presidential Cancer Panel, Devra Davis, founder for the Center for Environmental Oncology, Lloyd Morgan of the Central Brain Tumor Registry say that we are at the beginnings of a major brain tumor and cancer epidemic from cell phones
* studies link cell phone use to gliomas, meningiomas, acoustic neuromas, parotid gland tumors, tinnitus, sperm count drops, testicular cancer, decreased performance on tests, cognitive processing problems including but not limited to ADHD.
* the WHO acknowledges that 3% of the world population suffers from electrohypersensitivity and cannot tolerate proximity to cell phones, cell towers, wi-fi and other forms of electromagnetic pollution

The FCC needs to preserve wired last mile service. The big picture here is that utilities are trying to force consumers to go wireless; have phone service and internet delivered wirelessly exclusively, and have wireless smart meters put on to meter electricity useage. Smart meters, which have been rolled in by some utilities in New York State are projected to exceed the paltry FCC violations which even the federal Interagency Working Group on Radiofrequency Radiation deems to be non-protective of human health (see: Assessment of Radiofrequency Microwave Radiation Emissions from Smart Meters) http://sagereports.com/smart-meter-rf/

All of this wireless radiation is a known mutagenic carcinogen (per Dr. David O. Carpenter of the U.S. Presidential Cancer Panel) and levels of it should not be increased in public places. Long term public infrastructure investments in this country should use wired technology, not wireless. In light of problems with cell phones, cell towers and similar sources of continuous exposure to microwave radiation, it does not make sense to increase levels of RFR in public places and certainly not in peoples' homes.

NOTES on FCC PROPOSAL document:

FCC NOTICE OF PROPOSED RULEMAKING ON "CONNECT AMERICA FUND"
FCC 11-13
http://www.fcc.gov/Daily_Releases/Daily_Business/2011/db0209/FCC-11-13A1.pdf

Comments due April 18, 2011 Reply comments due May 23, 2011

Overview: Broadband delivered via wire, fiberoptic, cable or even satellite does not pose a health hazard from radiation. Wireless broadband that powers cell phone, video conferencing, wireless computer connections, etc emits increasing amounts of EMR 24/7. This proposal is for all technologies that deliver broadband to compete to deliver broadband 24/7 for the least cost.

Existing Universal Service Fund for Phone Service to be converted to funding broadband for the 24 million Americans with no access. In order to let most people in the US have phone service, the "Universal Service Fund" was created. It subsidizes phone service in areas that would otherwise not have phone service because of the high cost. From 1998 to today, the Universal Service Fund has grown from $2.3 billion to almost $9 billion. At first, consumers were "taxed" 5.53 % of interstate revenues to support this fund. This "tax" has now shot up to 15.5 %.
The FCC is proposing phasing out all this funding for just telephone service and paying the $9 billion fund to those companies that can provide broadband to everyone within various census blocks at the lowest cost through reverse auctions.

The FCC promises to provide a "National Broadband Map" to show where show where the funds to promote broadband would be targeted in the First Phase of the Connect America Fund. Para 261 p.91

The FCC seems to envision using "wired" or "fixed" networks to get the signal to cell towers and then using cell towers to get most of the signal elsewhere combined with Wi Fi in every home to promote "mobile broadband connectivity." #4 See diagrams at Para 117 pg 43-44

There are no references to considering the impact of the wireless method for "the last Mile" of connection to homes to the health of people with electrosensitivity and implants we documented in our previous filing on broadband that is part of this docket.

"Technology Neutral" bidding. The FCC plan is for competitive bidding by all wired and wireless or combination of broadband technologies for providing broadband to all the different census blocks of population that do not have access in the country. The FCC may reserve satellite (which gives off very little EMR) for the most difficult to reach places. Para #104 pg 39. The FCC plans to authorize and fund the provider of whichever technology comes up with the least expensive plan for each census block. We are not able to tell which census blocks are targeted with this funding but it appears that the FCC is moving toward requiring that all providers give broadband rather than just phone service.
ie-wired will be competing with wireless and the consumer gets no say in which technology is delivered to their home.

The FCC notes that 27 % of adults live in households with only wireless phones. Para # 8

Health: There is no discussion or consideration of the adverse effects of wireless broadband radiation to health or those with medical implants that may malfunction from this radiation.

The FCC seeks to "limit the contribution burden on households" Para 80 pg 31